Radiation-induced toxicity in prostate cancer: prediction and impact on quality of life

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Radiation-induced toxicity in prostate cancer: prediction and impact on quality of life

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Chapter 1: General Introduction

Prostate cancer is the second most common cancer in men worldwide, with an incidence of 1.1 million in 2012 [1]. In the Netherlands, prostate cancer is the most common cancer among men, with an incidence of 11,683 in 2017. As age is the most important risk factor for the development of prostate cancer and since the population is ageing, the incidence in the Netherlands is expected to increase in the near future and beyond [2] [3].

Taking this increase into account, treatment of prostate cancer will require extra attention in the near future. The decision-making process in prostate cancer treatment has traditionally been based upon two outcomes: the level of tumour control (and or survival) and the probability of developing side effects for a certain treatment. Late radiation-induced side effects are particularly relevant clinically, and these may have an impact on quality of life for prostate cancer survivors.

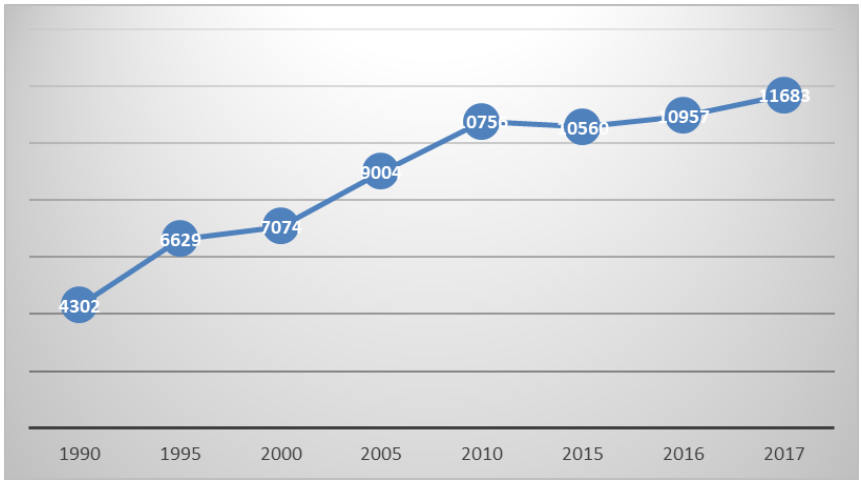

Figure 1: Incidence of prostate cancer in the Netherlands. www.cijfersoverkanker.nl

Prostate cancer treatment

Curatively intended prostate cancer treatment may involve radical prostatectomy, brachytherapy or external beam radiotherapy with or without adjuvant hormonal therapy. Evidence for which treatment is best has not been established by randomized trials in which these treatment modalities have been directly compared [4]. Treatment decisions are commonly based on the assumption that cure rates obtained with the different modalities are similar in low-risk disease (T1c-T2a, Gleason score <7, iPSA <10 ng/mL) irrespective of treatment modality. The only randomized trial on the efficiency of prostate cancer radiotherapy concerned patients with localized and mainly locally advanced prostate cancer (outside prostatic capsule) [5]. A significant reduction was found in prostate cancer specific mortality from 23.9% with hormonal treatment only to 11.9% with hormonal treatment in combination with radiotherapy.

Prostatectomy, external beam radiotherapy and brachytherapy all offer the opportunity to decrease prostate cancer related death [4]. The evidence for neo-adjuvant hormonal therapy regarding tumour control is present for locally advanced prostate cancer [6]. Recently, research has shown a significant improvement in biochemical disease-free survival (HR 0.52) for intermediate (T2b-c, of Gleason score 7) and high risk (T3, of Gleason score >7, or iPSA >20 ng/mL) prostate cancer patients treated with adjuvant hormonal therapy [7]. Finally, dose escalation in external beam radiotherapy has resulted in increased biochemical tumour control [8]. However, the down side of target dose escalation is an increase of dose to organs-at-risk adjacent to the prostate consequently, more radiation-induced side effects.

Radiation induced side effects

As the prostate is adjacent to the bladder and anorectum, irradiating the prostate results in unintended co-irradiation of these organs at risk. Consequently, side effects may occur, which are traditionally divided into gastrointestinal and genitourinary side effects. Gastrointestinal side effects include rectal bleeding, faecal incontinence, diarrhoea, increase in stool frequency, mucus loss and rectal pain. Genitourinary side effects include urinary incontinence, haematuria, and frequent micturition, pain during voiding and sexual dysfunction. From a clinical point of view, rectal bleeding is mostly considered of high importance, as it may require transfusions, although the need for these is rare [9]. From a patient's perspective, other side effects such as urinary or faecal incontinence may be more important as these may have a marked impact on daily functioning.

Radiation-induced side effects can be assessed using different grading systems [10]: The Radiation Therapy Oncology Group (RTOG) [11], Late Effects of Normal Tissue Subjective, Objective, Medical management and Analytic evaluation of injury (LENT-SOMA) [12] and Common Terminology Criteria for adverse events (CTCAE) [13]. The RTOG and CTCAE are the most commonly used grading systems in prostate cancer treatment. The CTCAE grading system provides an organ-specific list with physician-rated measurements for each specific complaint and accompanying grading, while the RTOG grading provides only a more general classification for some endpoints of prostate cancer treatment. This is the main reason for the application of the CTCAE toxicity scoring system at our department in the standardized follow-up program (SFP) for prostate cancer patients.

To reduce the risk of both gastrointestinal and genitourinary side effects, information on the relation between complication risk and dose-volume parameters of bladder and anorectum is crucial [9]. The relationship between 3D dose distributions and the risk of a given side effect is generally described by Normal Tissue Complication Probability (NTCP) models. These may contain dose-volume parameters and other baseline characteristics such as patient- tumour- and treatment-related features. NTCP models can be used for different purposes: They can be used to estimate the risk of developing a certain complication for a given patient based on the dose distribution and other predictors included in the model [14]; they can also be used to guide treatment planning optimization; and they can be used to identify which patients may benefit most from new and more complex radiation delivery techniques, such as protons [15].

In the Netherlands, proton therapy is now gradually introduced for different tumour sites. Selection of patients is based on the so-called model-based approach [14]. In this approach, the best possible photon plan is compared with the best possible proton plan to calculate the dose distributions in the most relevant

organs at risk and subsequently to assess the difference in dose between the two modalities (ΔDose). In addition, to determine the clinical relevance of ΔDose, NTCP-models are used to translate ΔDose into ΔNTCP, i.e. the expected benefit in terms of the risk reduction for a given side effect. When this is done for more than one radiation-induced side effect, a so-called ΔNTCP-profile can be produced, which can be considered as a biomarker for the expected benefit of protons compared to photons for each individual patient. In the Netherlands, a consensus has been reached on the ΔNTCP-thresholds depending on the grading of the toxicities. For grade 2, 3 and 4/5, ΔNTCP-thresholds should be ≥10%, ≥5% and ≥2%, respectively, to quality for proton therapy. However, a national indication protocol to select prostate cancer patients for proton therapy is currently not yet available.

Unmet needs

One of the requirements of the model-based approach is the availability of high quality multivariable NTCP-models in order to be able to translate ΔDose into a ΔNTCP-profile. To be suitable for model-based selection, NTCP-models should meet a number of important quality criteria, including:

1. Toxicity scoring should be done prospectively, as retrospective assessment generally results in an underestimation of radiation-induced toxicity;
2. The number of patients and events should be sufficient;
3. NTCP-models should be multivariable, not only including dose-volume parameters but also other characteristics that are independent predictors for toxicity or may be confounders or effect modulaters for the dose-volume factors;
4. There should be a clinical decision rule, i.e. an equation, nomogram or graph that can be used to calculate NTCP-values for individual patients based on the dose distributions and other pre-treatment predictors;
5. The quality of the model in terms of model performance should be assessed (e.g. discrimination and callibration);
6. Internal validation should be performed to correct for overfitting;
7. Preferably external validation should be done in an independent patients cohort to test the generalisibility of the model.

When we started this project, the number of published NTCP-models did not meet most of these criteria. The department of Radiation Oncology at UMCG has a long tradition of prospective assessment of radiation-induced toxicity and quality of life in different tumour sites, including of prostate cancer patients. The data from this prospective data registration program offers unique opportunities to develop multivariable NTCP-models and to investigate quality of life among patients treated with radiotherapy.

Outline of this thesis

The aims of this thesis were to investigate the course of quality of life among prostate cancer patients treated with radiotherapy, to investigate which side effect has the largest impact on quality of life and

ultimately to develop multivariable NTCP-models for prostate cancer patients treated with definitive radiotherapy.

Chapter 2 presents the difference in quality of life between prostate cancer survivors and a normative cohort. Using a mixed model statistical analysis, the longitudinal effects of radiotherapy can be appraised. In this case-control study, special attention was given to comorbidity, which is present in the majority of the elderly population.

Chapter 3 describes the impact of genitourinary and gastrointestinal side effects on quality of life. Different aspects of quality of life were analysed by means of a multivariate analysis of variance (MANOVA). In this analysis, functioning scales and relevant symptom scales were analysed in one single analysis, taking into account the interdependency of the scales.

Chapter 4 reports on the relationship between dose volume parameters of the anorectum and gastro-intestinal side effects. In contrast to current literature on prostate cancer irradiation, in this study different unique dose-volume parameters were related to different unique endpoints. The anorectum was divided into smaller substructures and additional Regions of Interest (ROI) were delineated in order to estimate the best prognostic model for each endpoint.

In **chapter 5**, a similar analysis was performed for genitourinary side effects by dividing the bladder into smaller substructures. Finally, for each endpoint a multivariable NTCP model was estimated. In these studies, a data-driven approach was used to build models, whereas knowledge-based models are another commonly used option to build models.

The findings of this thesis are discussed and summarized in **Chapter 6**. A Dutch translation of the summary is provided in **Chapter 7**.

References

[1] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11, France: International Agency for Research on Cancer; 2013. Available from: http://www.globocan.iarc.fr, accessed on 08/01/2017.

[2] Signaleringscommissie Kanker van KWF kankerbestrijding. Kanker in Nederland tot 2020: Trends en prognoses. Available from: https://www.kwf.nl/SiteCollectionDocuments/rapport-Kanker-in-Nederland-tot-2020.pdf, accessed on 12/01/2019.

[3] IKNL. Cijfers over kanker. Available from: www.cijfersoverkanker.nl. Accessed on 12/01/2019.

[4] Attard G, Parker C, Eeles RA, Schröder F, Tomlins SA, Tannock I, Drake CG, de Bono JS. Prostate cancer. Lancet 2016; 387:70-82.

[5] Widmark A, Klepp O, Solberg A, Damber J, Angelsen E, Fransson P, Lund J, Tasdemir I, Hoyer M, Wiklund F, Fosså SD, for the Scandinavian Prostate Cancer Group Study 7 and the Swedish Association for Urological Oncology 3. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 2009;373:301-08.

[6] Kumar S, Shelley M, Harrison C, Coles B, Wilt TJ, Mason M. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer (Review). Cochrane Library 2006;(4):CD006019.

[7] Bolla M, Maingon P, Carrie C, Villa S, Kitsios P, Poortmans PMP, Sundar S, van der Steen-Banasik EM, Armstrong J, Bosset J, Herrera FG, Pieters B, Slot A, Bahl, Ben-Yosef R, Boehmer D, Scrase C, Renard L, Shash E, Coens C, van den Bergh ACM, Collette L. Short androgen suppression and radiation dose escalation for intermediate- and high-risk localized prostate cancer: Results of EORTC Trial 22991. Journal of clinical oncology 2016; (34):1758-1756.

[8] Zelefsky MJ, Pei X, Chou JF, Schechter M, Kollmeier M, Cox B, et al. Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. Eur J Urol 2011;60:1133–9.

[9] Budäus L, Bolla M, Bossi A, Cozzarini C, Crook J, Widmark A, Wiegel T. Functional outcomes and complications following radiation therapy for prostate cancer: A critical analysis of the literature. European Urology 2012; (61); 112-117.

[10] Laan van der HP, Bergh van den ACM, Schilstra C, Vlasman R, Meertens H, Langendijk JA. Grading-system-dependent volume effects for late radiation-induced rectal toxicity after curative radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1138–45.

[11] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–1346.

[12] Pavy JJ, Denekamp J, Letschert J, et al. EORTC Late Effects Working Group. Late effects toxicity scoring: The SOMA scale. Radiother Oncol 1995;35:11–15.

[13] Trotti A, Colevas AD, Setser A, Rusch V, Jaquesc D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176–81.

[14] Langendijk JA, Lambin P, De Ruysscher D et al.. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol 2013; 107: 267-273.

[15] Widder J, van der Schaaf A, Lambin P, Marijnen CAM, Pignol J, Rasch CR, Slotman BJ, Verheij M, Langendijk JA. The quest for evidence for proton therapy: Model-based approach and precision medicine. Int J Radiat Oncol Biol Phys 2016; 1: 30-36.

Chapter 2: Quality of life among prostate cancer patients: a prospective longitudinal population-based study.

W. Schaake, M. de Groot, W.P. Krijnen, J.A. Langendijk, A.C.M. van den Bergh

Radiotherapy and Oncology: 2013 Aug;108(2):299-305

Abstract

Purpose
To investigate the course of quality of life (QoL) among prostate cancer patients treated with external beam radiotherapy and to compare the results with QoL of a normal age-matched reference population.

Patients and methods
The study population was composed of 227 prostate cancer patients, treated with radiotherapy. The EORTC QLQ-C30 was used to assess QoL before radiotherapy and six months, one year, two years and three years after completion of radiotherapy. Mixed model analyses were used to investigate longitudinal changes in QoL. QoL of prostate cancer patients was compared to that of a normative cohort using a multivariate analysis of covariance.

Results
A significant decline in QoL was observed after radiotherapy ($p < 0.001$). The addition of hormonal therapy to radiotherapy was associated with a lower level of role functioning. Patients with coronary heart disease and or chronic obstructive pulmonary disease or asthma had a significantly worse course in QoL. Although statistically significant, all differences were classified as small or trivial.

Conclusion
Prostate cancer patients experience a small worsening of QoL as compared with baseline and as compared with a normal reference population. As co-morbidity modulates patients' post-treatment QoL, a proper assessment of co-morbidity should be included in future longitudinal analyses on QoL.

Introduction

Quality of life (QoL) among prostate cancer patients is an important outcome measure of therapy, providing relevant information on how patients experience their functioning in daily life after treatment. Although high survival rates after curative radiotherapy have been reported [1], side effects like fecal or urinary incontinence may occur as a result of prostate radiotherapy. As a substantial proportion of prostate cancer patients report these side effects during follow-up [1–4], QoL may be transiently or permanently reduced.

QoL after therapy may not only be affected by the development of side effects, but also by baseline measures of QoL, e.g., due to the presence of co-morbidity. A previous study showed that as much as 53% of the population aged 55 years and older had at least onemild or severe chronic condition [5]. The question arises as to whether co-morbidity plays an important role in the changes of QoL after treatment among prostate cancer patients. Although QoL has been measured widely among prostate cancer patients [6–8], baseline measures of QoL and the effect of co-morbidity have not been consistently taken into account.

Interpretation of the results of QoL studies is challenging and could be facilitated by comparing the results with QoL measured in the general population in order to determine the additional functional impairment and symptom burden associated with prostate cancer and its treatment [9]. Normative data not only enables comparing QoL scores of prostate cancer patients against those obtained in the normative population, but also offers the opportunity to analyze the impact of covariates such as age and co-morbidity [10].

Therefore, the objective of the current study was twofold. The primary objective was to investigate to what extent QoL changes after completion of curative radiotherapy among prostate cancer patients, with special attention to the influence of baseline QoL and co-morbidity. The second objective was to investigate to what extent QoL of prostate cancer patients differs from that of a normal reference population.

Patients and methods

Study design, patient and normative cohort selection, treatment

The study population of this prospective cohort study was composed of 227 patients with localized or locally advanced prostate cancer. All patients were treated at the University Medical Center Groningen and were originally included in two multicenter prospective randomized studies. Ninety-nine patients were included in the European Organization for Research and Treatment of Cancer (EORTC) 22961 trial and 128 patients in the EORTC 22991 trial. The EORTC 22961 trial started in 1997 and was designed to evaluate the influence of adjuvant hormonal treatment with an LHRH (luteinizing-hormone-releasing hormone) analog in patients with locally advanced prostate cancer treated with 3D-CRT. The EORTC 22961 protocol included patients with non-metastatic T1c- T2bN1-2/pN1-2 (after pelvic lymphadenectomy) or T2c-T4N0-2 (UICC 1992 TNM classification) histologically confirmed adenocarcinoma of the prostate.

Patients in the long arm (three years) received combined androgen blockade for a period of three years, while patients in the short arm received combined androgen blockade for a period of only six months [11].

In the EORTC 22991 trial, radiotherapy alone, either 3D-CRT or IMRT, was compared with the same radiotherapy combined with adjuvant hormonal therapy in localized T1b-c, T2a, N0, M0 prostatic carcinoma. Patients in the adjuvant hormonal arm started hormonal treatment one week before radiotherapy with antiandrogens each day for a period of one month and additionally two injections of LHRH during the next six months [12]. For the purpose of the current analysis, only patients biochemically failure free at the time of QoL assessments were eligible.

All patients were treated with external beam radiotherapy. A planning CT of all patients was obtained in treatment position (supine). The clinical target volume (CTV) was defined as the prostate and the seminal vesicles. Radiotherapy was delivered with linear accelerators using photons with either 3-dimensional conformalradiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT). Patients were treated 5 times a week to a total dose of 70 Gy (3D-CRT) or 78 Gy (IMRT).

The patient cohort was compared to a normative cohort of male individuals from the PROFILES study [9]. QoL normative data were obtained from the Health and Health Complaints project from CentERdata. The CentERpanel cohort represents the Dutch-speaking population in the Netherlands, including those without Internet access. From this panel a normative cohort of 519 men was selected, resulting in an age matched comparison between the patient cohort and the normative cohort.

Quality of life assessment

QoL was measured by means of the EORTC Quality of life Questionnaire C30 (EORTC QLQ-C30) [13] prior to the start of radiotherapy and subsequently at 6, 12, 24 and 36 months after completion of radiotherapy. The current analysis covered five QoL scales that were considered to be most likely affected by therapy and/or comorbidity, including global quality of life, physical functioning, social functioning, emotional functioning and role functioning. In addition, six symptom scales were analyzed, including fatigue, pain, dyspnea, insomnia, constipation and diahrroea. QoL-scores were linearly converted to a scale ranging from 0 to 100, according to EORTC guidelines. For the functional and global health status/quality of life scales, higher scores represent better levels of functioning. For the symptom scales, higher scores represent a greater degree of symptoms.

Statistics

Changes in QoL before and after treatment were estimated by means of a mixed model analysis. The first advantage of a mixed model analysis over a standard analysis of variances (ANOVA) is that it takes into account variability between patients' (baseline) scores. Secondly, a mixed model ANOVA can deal better with missing values than the standard ANOVA model. Using a standard ANOVA model, one or more missing observations in one patient result in a complete loss of all data of that particular patient, while using the mixed model approach only the missing observations are lost. Other factors included in the model were adjuvant hormonal therapy, radiotherapy technique and co-morbidity.

To investigate the clinical relevance of the longitudinal differences, the effect sizes were categorized as proposed in a meta-analysis by Cocks [14] into trivial, small, medium and large differences per scale. To investigate the differences between prostate cancer patients 3 years after treatment and the

normative cohort a multivariate analysis of covariance (MANCOVA) was used. Unbalanced distribution of patient characteristics (Table 1) was accounted for by means of the addition of covariates into the model. To investigate the clinical relevance of the differences with the normative comparison, the effect sizes were categorized as proposed by Cocks [15]: trivial, small, medium or large difference per scale. A p-value of 0.05 was considered to be statistically significant.

Table 1: Patients and normative cohort characteristics

		Patients (%) N= 227		Norm (%) N= 519		
Heart disease		49	(22)	97	(19)	
COPD and asthma		24	(11)	46	(9)	
Hypertension		62	(27)	176	(34)	*
Stroke		5	(2)	4	(1)	
Diabetes		21	(9)	47	(9)	
Peptic ulcer		4	(2)	8	(2)	
Kidney disease		4	(2)	9	(2)	
Liver disease		0	(0)	2	(0.4)	
Thyroid disease		3	(1)	6	(1)	
Age ≤70		134	(59)	360	(69)	*
Tumor classification						
	T1	85	(37)			
	T2	68	(30)			
	T3	74	(33)			
PSA						
	< 10	50	(22)			
	10-20	97	(43)			
	20-40	60	(26)			
	>40	20	(9)			
Adjuvant treatment						
	Radiotherapy only	71	(31)			
	Radiotherapy and hormonal therapy	156	(69)			
Radiotherapy Modality						
	IMRT	70	(31)			
	3D-CRT	157	(69)			

* Statistically significant at 0.05 using Fisher exact test

Results

Sample description and compliance

At baseline, 200 out of the 227 patients completed the QoL questionnaire. The compliance rate six months after treatment was 95% (210 out of 221 patients alive), 96% after one year (208 out of 216 patients alive), 95% after two years (202 out of 213 patients alive) and 88% three years after radiotherapy (184 out of 209 patients alive). The majority of patients was treated with adjuvant hormonal therapy and 3D-CRT. The median age was 70 years (range 53–85).

Baseline patient characteristics and normative cohort characteristics are listed in Table 1. The prevalence of co-morbidities did not differ significantly between the patients and the normative cohort, except for hypertension. Although the patient and normative cohort had the same age range, the average age of the prostate cancer patient cohort (69.2)wassignificantly higher than that of the normative cohort (66.6, $p < 0.001$). This imbalance was accounted for by adding age as a covariate into the statistical analysis.

Longitudinal effects in the patient cohort

The mixed model analysis revealed that in general, patients' post-treatment QoL was worse as compared to pre-treatment QoL (Figs. 1 and 2). Post-treatment global QoL and emotional functioning did not differ from baseline (Table 2). A minimal but statistically significant decrease was observed for physical functioning. The scores of role- and social functioning decreased after treatment and reached a plateau at 6 months after radiotherapy. Five out of six symptom scales changed relative to baseline. Fatigue, dyspnea and insomnia increased after treatment with maximum levels of impairment at six months after treatment. The level of constipation and diarrhea after radiotherapy increased compared to baseline in particular at one year after radiotherapy. Although the pvalues for time effects were statistically significant, the absolute differences were relatively small. The maximum mean difference was 8.02 for insomnia. Using the criteria from Cocks [14] for clinical relevance, all longitudinal differences observed were considered trivial or small.

No differences in QoL were found between 3D-CRT and IMRT patients. QoL was significantly affected by two co-morbid conditions. First ''COPD and asthma'', which affected global quality of life, physical-, role- and social functioning ($p < 0.003$). These patients also reported more fatigue, dyspnea and insomnia ($p < 0.02$). Second, coronary heart disease, which affected global quality of life, role- and social function ($p < 0.03$). Additionally these patients reported more dyspnea ($p < 0.01$). Adjuvant hormonal treatment affected both physical functioning ($p < 0.001$) and constipation ($p = 0.043$). Apart from these main effects, three significant interaction terms were found, indicating that some patient or treatment characteristics affected the course of QoL after treatment (Fig. 3a). First, patients treated with hormonal therapy had worse role functioning after treatment than patients without hormonal treatment. For patients treated with short-term adjuvant hormonal therapy, a decline in role functioning was noted at six months after radiotherapy. For patients with long-term hormonal therapy a similar decline was observed at 6 months after radiotherapy, followed by a further deterioration at 12 months after radiotherapy. However, eventually both groups returned to similar role functioning scores at 36 months after

Table 2: Mixed model analysis for the longitudinal comparison of QLQ-C30 functioning and symptom scales in the patient cohort. Clinical relevance was categorized as proposed by Cocks (2012): trivial differences ( ), small differences (*), medium differences (**) and large differences (***)

		Mean score difference relative to baseline				P-value			
QLQ-C30 scales		6 months	12 months	24 months	36 months	Time	Time by HT	Time by COPD	Time by CHD
Functioning									
	Global Quality of Life	--	--	--	--	*N.S.*	*N.S.*	*N.S.*	*N.S.*
	Physical functioning	-2.87	-2.49	-3.41	-4.04	<0.001	*N.S.*	*N.S.*	*N.S.*
	Role functioning	-3.75	-4.62	-4.97	-5.11	0.018	0.039	0.033	*N.S.*
	Emotional functioning	--	--	--	--	*N.S.*	*N.S.*	*N.S.*	*N.S.*
	Social functioning	-3.90	-2.94	-4.77	-4.95	<0.001	*N.S.*	*N.S.*	0.018
Symptom									
	Fatigue	5.98 *	5.58 *	5.34 *	4.70	<0.001	*N.S.*	*N.S.*	*N.S.*
	Pain	-2.48	-2.78	-0.33	-0.46	0.036	*N.S.*	*N.S.*	*N.S.*
	Dyspnoea	5.52 *	5.40 *	5.64 *	5.41 *	<0.001	*N.S.*	*N.S.*	*N.S.*
	Insomnia	8.02 *	4.76 *	1.30	3.70 *	<0.001	*N.S.*	*N.S.*	*N.S.*
	Constipation	1.56	5.38 *	3.51	4.11	<0.001	*N.S.*	*N.S.*	*N.S.*
	Diahrroea	3.01	5.13 *	2.87	1.13	0.001	*N.S.*	*N.S.*	*N.S.*

HT: adjuvant hormonal therapy
COPD: chronic obstructive pulmonary disease
CHD: congestive heart disease

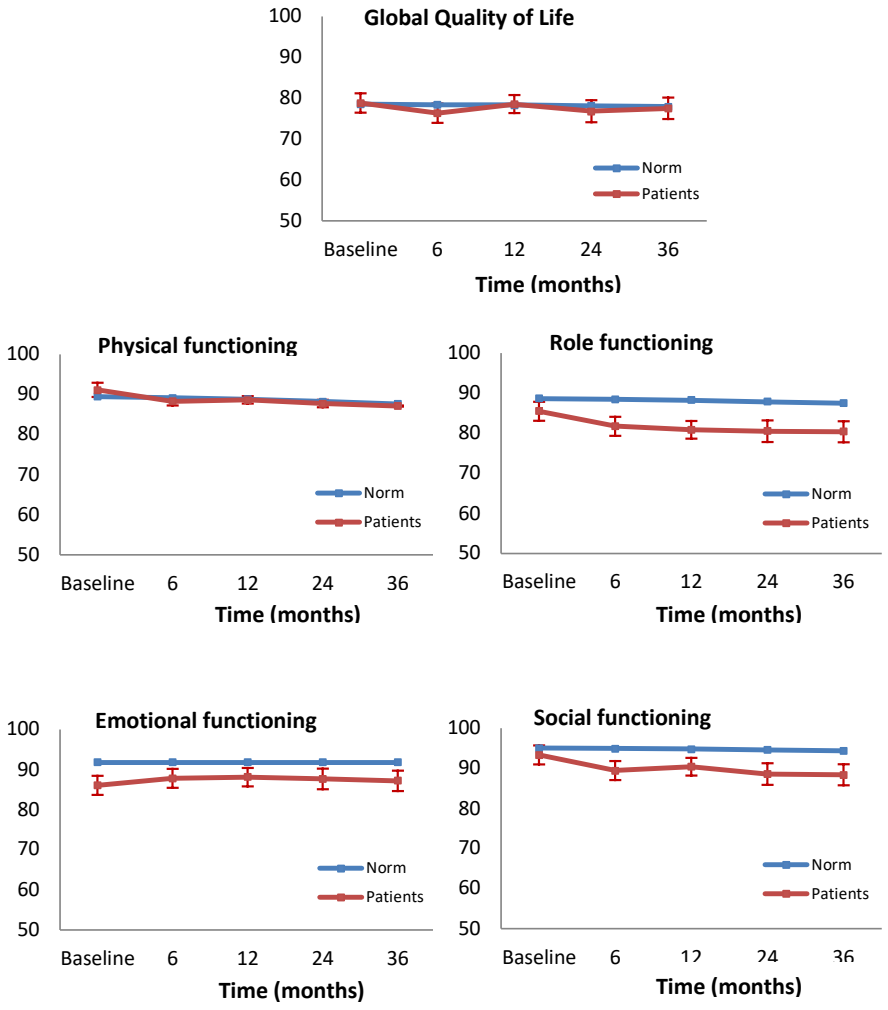

Figure 1: Mean EORTC QLQ-C30 functioning scale scores of prostate cancer patients relative to the normative cohort: higher scores represent a better level of functioning

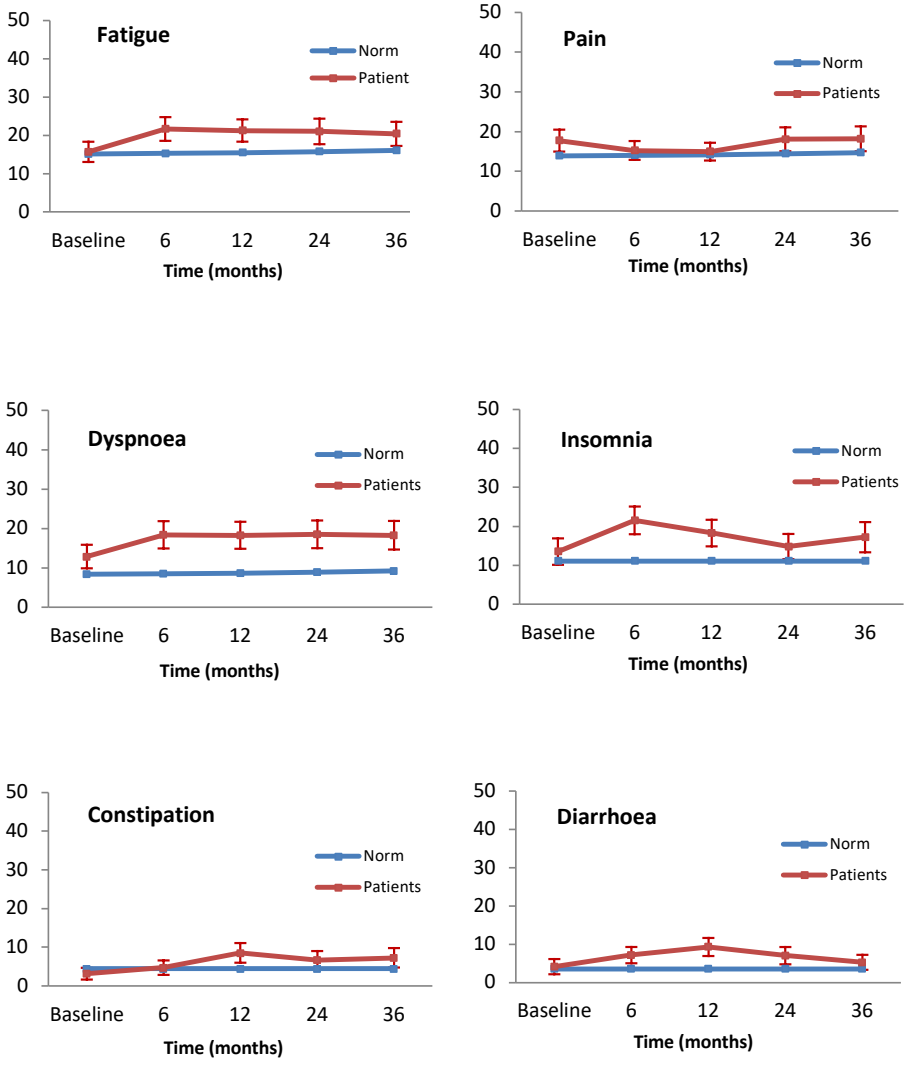

Figure 2: Mean EORTC QLQ-C30 symptom scale scores of prostate cancer patients relative to the normative cohort: higher scores represent a greater degree of symptom

radiotherapy as compared to patients treated without hormonal treatment. Second, patients with COPD or asthma did significantly worse on role functioning than patients without this co-morbid disease (Fig. 3b), especially 12 months after radiotherapy patients with COPD or asthma had a lower role functioning than patients without this co-morbidity. Finally, the patients with coronary heart disease did significantly worse with regard to social functioning compared to patients without coronary heart disease (Fig. 3c).

Comparison with the normative cohort

Three factors were entered into the MANCOVA model as covariates, as they significantly affected QoL including ''age'', ''CHD'' and ''COPD or asthma'' (Table 3). This analysis revealed a statistically significant difference in QoL between the prostate cancer patient cohort (3 years after treatment) and the normative cohort. ''CHD'' and ''COPD and asthma'' also significantly affected QoL.

To get insight into which QoL scales were affected most, we focused on the differences between the two groups on every single scale. Prostate cancer patients did significantly worse on three out of five functioning scales as compared to the normative cohort, i.e., role-, emotional- and social functioning. Prostate cancer patients also reported more dyspnea and insomnia than males from the normative cohort. The clinical relevance of these differences was classified as trivial or small, except for dyspnea, which was classified as a medium effect.

Discussion

The main objective of this study was to determine the course of QoL of prostate cancer patients after curative radiotherapy. Our study shows that QoL deteriorates most during the first six months after treatment and then remains more or less unchanged up to three years after completion of radiotherapy. In addition, we found that the QoL of prostate cancer patients three years after radiotherapy is worse than QoL of males from a normative population. Although both longitudinal and population differences show statistical significance, the clinical relevance of these differences was small and should be considered trivial.

The main strengths of the current study are the baseline measurements, the long-term follow-up, the high compliance rates, the population-based design, and the adjustment for comorbidities. It is important to include baseline levels of QoL, as the course of QoL over time may depend on baseline scores [7]. In another study small, but non-significant deteriorations in patients' QoL, as measured by the SF-36 were found [16]. The cross-sectional design of that study required longitudinal confirmation to account for differences in baseline measurements between patients. A proxy for baseline measurements of QoL is to ask patients to recall their QoL at baseline [17]. However, prostate cancer patients tend to remember their baseline QoL as being better than it actually was [18], indicating that an actual assessment of QoL at baseline is necessary. With the inclusion of actual baseline measurements, the current study showed that QoL among prostate cancer patients indeed deteriorated over time, but also that these differences were relatively small and have little clinical importance.

Two other studies [7–8] covered patients with a maximum follow-up time of two years, while Pardo [19] and Hoskin [20] analyzed the QoL up to 3 and up to 10 years, respectively. The question may arise as to whether 36 months is an adequate follow-up time in longitudinal prostate cancer research. As late radiation-induced side effects occur or progress further over time [3] it may be important to assess

QoL after two years, in order to be able to account for the possible effect of these side effects on QoL. In accordance with the outcome of a large randomized trial [21], the current study shows that quality of life is lower in the first 6 months after treatment and remains relatively unchanged up to three years after radiotherapy.

As the compliance rates in the current study are high, the risk of selection bias as a consequence of missing data is small. However, exclusion of patients with biochemical failure prohibits the results to be generalized to all prostate cancer patients treated with radiotherapy. In this regard, it should be stressed that 35% of the patients with biochemical failure will develop metastatic disease within 8 years from the time of prostate-specific antigen elevation. This elevation may cause significant anxiety for patients which negatively affects QoL [22].

The population-based design of the present study not only enabled comparison of the QoL scores of patients against those obtained in the normative population, but also offered the opportunity to analyze the impact of covariates such as age and comorbidities. According to recommendations defined by Crosby [23], anchoring patient data to normative data indicates whether the differences before and after treatment are large, relative to a normative population. As both longitudinal differences and normative differences were small, our conclusion is supported on two fronts: a post-treatment to baseline contrast and a posttreatment to norm contrast. Co-morbidities significantly affected QoL of prostate cancer patients, which is in line with results obtained in other patient groups [9,24–25]. As prostate cancer is a malignant disease predominantly found among elderly patients and because the incidence of co-morbidity increases with age, it is especially important to account for this potential confounder when analyzing QoL among prostate cancer patients. However, in recent studies reporting on QoL after radiotherapy [6–8] the possible impact of co-morbidity had not been taken into account. As co-morbidities were retrospectively scored in the current research, an underestimation of the incidence of co-morbidities is possible. Despite this limitation, our study shows interesting findings concerning co-morbidities. That is ''COPD and asthma'' and ''coronary heart disease'' significantly affect role- and social functioning among prostate cancer patients. This is in accordance with two studies on the impact of co-morbidities on QoL of prostate cancer patients [26–28]. To explain the falling course in QoL of patients with COPD, we retrospectively analyzed these patients' doctor visits to other departments. There, we observed an increase in COPD exacerbations around twelve months after radiotherapy and additionally, an increase of the impact of dyspnea on role functioning. This indicates that COPD patients may be bothered more by dyspnea at twelve months than at baseline, finally resulting in a decreased role functioning. Future research should emphasize more on this synergistic effect of COPD and radiotherapy on QoL in order to prevent a further decline in QoL among males with these risk factors.

Two issues in this research require extra attention. First, as QoL assessment has an inherent subjective nature, possible changes of patients' internal standards, changing values and conceptualization of QoL may well have an effect on patients' scoring of QoL. This phenomenon is referred to as response shift, which may explain the relatively small changes in QoL [29]. A subset of patients may also rate their HRQoL as always good (or bad) and always improving (or declining), reflecting a dispositional optimism (or pessimism). This general methodological concern may be a possible limitation in determining a minimally important difference in change score in al HRQoL studies [30]. Another important issue is the course of patients' sexual functioning. Unfortunately, sexual functioning was not assessed in our study. The odds of erectile dysfunction increase after radiotherapy [31,32] and hormonal therapy has an additional negative

impact on sexual functioning [33]. Therefore, we recommend further longitudinal studies to include sexual functioning as an outcome measure into the analysis.

Different criteria can be used to analyze the clinical relevance of differences between patients. This is the first study that used Cocks' criteria to evaluate QoL changes in prostate cancer patients. Cocks' criteria are based on expert opinions and metaanalysis. One advantage of these criteria is that a distinction is made between longitudinal differences [14] and cross-sectional differences [15]. Another advantage of Cocks' criteria is that for each QoL scale a unique division into categories is made. This is in contrast with criteria as proposed by Osoba [34], who made the same division into categories for all QoL scales: no difference (<5 points), little difference (5–10 points), moderate difference (10–20 points) and large difference (>20 points). Although the definition of clinical relevance according to Cocks is different from that of Osoba, our results suggest similar conclusions from either set of definitions.

As both longitudinal and population differences were of small clinical importance, we conclude that curative radiotherapy offers the opportunity to treat prostate cancer in an effective manner, without substantially affecting QoL.

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References

[1] Spratt DE, Pei X, Yamada J, et al. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2013;85:686–92.

[2] Al-Mamgani A, Heemsbergen WD, Levendag PC, et al. Subgroup analysis of patients with localized prostate cancer treated within the Dutch-randomized dose escalation trial. Radiother Oncol 2010;96:13–8.

[3] Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinarytoxicities after three-dimensional conformal radiotherapy and intensitymodulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1124–9.

[4] Peeters STH, Heemsbergen WD, Koper PCM, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicentre randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 2006;24:1990–6.

[5] van Oostrom SH, Picavet HSJ, van Gelder BM, et al. Multimorbidity and comorbidity in the Dutch population-data from general practices. BMC Public Health 2012;12:715.

[6] Lips I, Dehnad H, Kruger AB, et al. Health-related quality of life in patients with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs. 70 Gy conformal radiotherapy in a prospective and longitudinal study. Int J Radiat Oncol Biol Phys 2007;69:656–61.

[7] Ferrer M, Suárez JF, Guedea F, et al. Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;72:421–32.

[8] Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Eng J Med 2008;358:1250–61.

[9] van de Poll-Franse LV, Mols F, Gundy CM, et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. Eur J Cancer 2011;47:667–75.

[10] Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer 2001;37:1331–4.

[11] Bolla M, de Reijke T. Long term adjuvant hormonal treatment with LHRH analogue versus no further treatment in locally advanced prostatic carcinoma treated by external irradiation and six months combined androgen blockage—a phase III study. EORTC Trial 22961. A joint trial of the EORTC Radiotherapy and EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC DATA CENTER. 1997.

[12] Bolla M. EORTC Radiotherapy Cooperative Group, three dimensional conformal radiotherapy alone vs three dimensional conformal therapy plus adjuvant hormonal therapy in localized T1b-c, T2a, N0, M0 prostatic carcinoma. A Phase III Randomized Study. EORTC PROTOCOL 22991. 2000.

[13] Aaronson N, Ahmedzai S, Bergman B, Bullinger M, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

[14] Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European organisation for the research and treatment of cancer quality of life questionnaire core 30. Eur J Cancer 2012;48:1713–21.

[15] Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for determination of sample size and interpretation of the European organisation for the research and treatment of cancer quality of life questionnaire core 30. J Clin Oncol 2011;29:89–96.

[16] Mols F, van de Poll-Franse LV, Vingerhoets AJ, et al. Long-term quality of life among Dutch prostate cancer survivors: results of a population-based study. Cancer 2006;107:2186–96.

[17] Potosky AL, Harlan LC, Stanford JL, et al. Prostate cancer practice patterns and quality of life. J Natl Cancer Inst 1999;91:1719–24.

[18] Litwin MS, McGuigan KA. Accuracy of recall in health-related quality-of-life assessment among men treated for prostate cancer. J Clin Oncol 1999;17:2882–8.

[19] Pardo Y, Guedea F, Aguiló F, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. J Clin Oncol 2010;28(31):4687–96.

[20] Hoskin PJ, Rojas AM, Ostler PJ, et al. Quality of life after radical radiotherapy for prostate cancer: a longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dos rate brachytherapy. Clin Oncol 2013;25:321–7.

[21] Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. N Eng J Med 2009;360:2516–27.

[22] Bruce JY, Lang JM, McNeel DG, et al. Current controversies in the management of biochemical failure in prostate cancer. Clin Adv Hematol Oncol 2012;10:716–22.

[23] Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 2003;56:395–407.

[24] Fosså SD, Hess SL, Dahl AA, et al. Stability of health-related quality of life in the Norwegian general population and impact of chronic morbidity in individuals with and without a cancer diagnosis. Acta Oncol 2007; 46:452–61.

[25] Janssen-Heijnen MLG, Houterman S, Lemmens VEPP, et al. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Critic Rev Oncol/Hematol 2005;55:231–40.

[26] Ramsey SD, Zeliadt SB, Hall IJ, et al. On the importance of race, socioeconomic status and comorbidity when evaluating quality of life in men with prostate cancer. J Urol 2007;177:1992–9.

[27] van de Poll-Franse LV, Kwan L, Reiter RE, et al. The influence of cardiovascular disease on health related quality of life in men with prostate cancer: a 4-year followup study. J Urol 2008;179:1362–7.

[28] van de Poll-Franse LV, Sadetsky N, Kwan L, et al. Severity of cardiovascular disease and health-related quality of life in men with prostate cancer: a longitudinal analysis from CaPSURE. Qual Life Res 2008;17:845–55.

[29] Schwartz CE, Sprangers MAG. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med 1999;48:1531–48.

[30] Cell D, Hahn EA, Dineen K. Meaningful change in cancer-specific quality of life scores: differences between improvement and worsening. Qual Life Res 2002;11:207–21.

[31] Mangar SA, Sydes MR, Tucker HL, et al. Evaluating the relationship between erectile dysfunction and dose received by the penile bulb: using data from a randomised controlled trial of conformal radiotherapy in prostate cancer (MRCRT01, ISRCTN47772397). Radiother Oncol 2006;80:355–62.

[32] Incrocci L. Sexual function after external-beam radiotherapy for prostate cancer: what do we know? Critic Rev Oncol/Hematol 2006;57:165–73.

[33] Pinkawa M, Piroth MD, Asadpour B, et al. Neoadjuvant hormonal therapy and external-beam radiotherapy versus external-beam irradiation alone for prostate cancer. A quality-of-life analysis. Strahlenther Onkol 2009; 185:101–8.

[34] Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44.

Chapter 3: The impact of gastrointestinal and genitourinary toxicity on health related quality of life among irradiated prostate cancer patients

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Abstract

Purpose

To determine the impact of late radiation-induced toxicity on health-related quality of life (HRQoL) among patients with prostate cancer.

Patients and methods

The study sample was composed of 227 patients, treated with external beam radiotherapy. Common Terminology Criteria for Adverse Events version 3.0 were used to grade late genitourinary and gastrointestinal toxicity. The European Organization for Research and Treatment of Cancer Quality of life Questionnaire C30 (EORTC QLQ-C30) was used to assess HRQoL at baseline, and 6, 12 and 24 months after completion of radiotherapy. Statistical analysis was performed using a multivariate analysis of variance (MANOVA).

Results

Urinary incontinence and rectal discomfort significantly affected HRQoL. The impact of urinary incontinence on HRQoL was most pronounced 6 months after radiotherapy and gradually decreased over time. The impact of rectal discomfort on HRQoL was predominant at 6 months after radiotherapy, decreased at 12 months and increased again 2 years after radiotherapy. No significant impact on HRQoL was observed for any of the other toxicity endpoints, or non-toxicity related factors such as hormonal therapy, radiotherapy technique or age.

Conclusion

Urinary incontinence and rectal discomfort have a significant impact on HRQoL. Prevention of these side effects may likely improve quality of life of prostate cancer patients after completion of treatment.

Introduction

Treatment of patients with localized or locally advanced prostate cancer may involve surgery, radiotherapy and adjuvant hormonal therapy. Although these treatment options result in high rates of tumor control, a substantial number of patients experience treatment related side effects. Side effects induced by prostate cancer treatment are typically expressed in the gastrointestinal (GI) and genitourinary (GU) tract (Table 1). Radiation oncologists currently focus on the prevention of these side effects by making adjustments in the treatment, based on the relationship between the dose to specific anatomical regions and the risk of a given side effect. The majority of studies that attempt to clarify this relationship included severe rectal bleeding as one of the primary endpoints in their analysis [1–4]. Although severe rectal bleeding is considered clinically relevant, the impact of mild or moderate side effects on patients' daily life is less evident.

As a result of radiation-induced side effects, patients might experience discomfort to such an extent that their health-related quality of life (HRQoL) is depressed [5]. Several studies showed that HRQoL in patients treated with definitive radiotherapy varies widely among individual patients [6–8]. This variation in HRQoL may be at least partly explained by differences in the occurrence and severity of the experienced side effects; severe toxicity is probable to result in lower levels of HRQoL. Lilleby et al. tested this hypothesis [9] but did not find any relationship between toxicity endpoints and HRQoL in their multivariate analysis. Two other studies [10,11] found a general impact of bowel, sexual and urinary symptoms on HRQoL. However, the impact of more specific endpoints, such as pain after treatment, is still unclear. Also the question arises to whether the possible impact of side effects varies over time.

To gain insight into the wellbeing of patients after prostate radiotherapy it is essential to know which and to what extent toxicity endpoints affect patients' HRQoL, in order to make decisions that may prevent a decline in HRQoL after definitive radiotherapy for prostate cancer. Therefore, the main objective of this study was to investigate the impact of radiation-induced toxicity on HRQoL.

Patients and methods

Patients and eligibility criteria

The study sample was composed of 227 prostate cancer patients treated with definitive radiotherapy. Patients had been included in two multicenter prospective randomized studies, 99 patients were included in the EORTC 22961 trial and 128 patients were included in the EORTC 22991 trial [12,13].

The EORTC 22961 trial started in 1997 and was designed to evaluate the influence of adjuvant hormonal treatment with an LHRH (luteinizing-hormone-releasing hormone) analog in patients with locally advanced prostate cancer treated with 3D-CRT. The EORTC 22961 protocol included patients with non-metastatic T1c-T2bN1-2/pN1-2 (after pelvic lymphadenectomy) or T2c-T4N0-2 (UICC 1992 TNM

Table 1: Late cumulative GU and GI toxicity according to the CTCAEv3.0 morbidity scale at two years after radiotherapy

		Grade 1	*Patients (%)*	*Grade 2*	*Patients (%)*	*Grade 3*	*Patients (%)*
GU-toxicity	*Urinary Incontinence*	occasional, pads not indicated	27.3	spontaneous, pads indicated	12.8	clinical intervention indicated	--
	Hematuria	asymptomatic	5.2	symptomatic, urinary catheter or bladder irrigation indicated	1.3	gross, requiring clinical intervention	--
	Dysuria	mild	25.1	moderate	7.5	severe	--
	Urinary frequency/nycturia	≤ 2 x normal	15.4	> 2 x normal/but < hourly	5.3	≥ 1x/hr, urgency, catheter indicated	0.4
GI-toxicity	*Fecal incontinence*	occasional use of pads required	2.2	daily use of pads required	0.1	requiring operative intervention	--
	Rectal bleeding	mild, intervention not indicated	13.7	moderate, medical intervention indicated	9.3	severe, transfusion or elective operative intervention indicated	1.8
	Rectal pain	mild	22.0	moderate, requiring medication	7.5	severe, requiring medication	--
	Stool-frequency	<4 stools per day over baseline	28.5	4-6 stools per day over baseline	3.5	≥ 7 stools per day over baseline	0.8

Abbreviations: GU = genitourinary; GI = gastrointestinal

classification) histologically confirmed adenocarcinoma of the prostate. Patients in the long arm (three years) received combined androgen blockade for a period of three years, while patients in the short arm received combined androgen blockade fora period of only six months.

In the EORTC 22991 trial, radiotherapy alone, either 3D-CRT or IMRT, was compared with the same radiotherapy combined with adjuvant hormonal therapy in localized T1b-c, T2a, N0, M0 prostatic carcinoma. Patients in the adjuvant hormonal arm started hormonal treatment one week before radiotherapy with antiandrogens each day for a period of one month and additionally two injections of LHRH during the next six months.

These trials were carried out according to local ethical legislations and informed consent was obtained from all patients. For the purpose of the current analysis, only patients that were biochemically failure free at the time of HRQoL assessment were included.

Radiotherapy

A planning CT of all patients was obtained in treatment position (supine). The clinical target volume (CTV) was defined as the prostate and the seminal vesicles. Radiotherapy was delivered with linear accelerators using photons with either three dimensional radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT). Patients were treated 5 times a week to a total dose of 70 Gy (3D-CRT) or 78 Gy (IMRT). Setup accuracy was verified during delivery by matching bony anatomy and setup errors were corrected by using a shrinking-action-level protocol [14].

HRQoL and toxicity assessment

HRQoL and toxicity were assessed prior to the start of radiotherapy and subsequently at 6, 12 and 24 months after completion of radiotherapy. HRQoL was measured by means of the European Organization for Research and Treatment of Cancer Quality of life Questionnaire C30 (EORTC QLQ-C30) [15]. The current analysis covered the HRQoL scales that were considered to be affected by GI and GU toxicity, including global quality of life, physical functioning, social functioning, emotional functioning, role functioning and the symptom scale fatigue. HRQoL-scores were linearly converted to a scale ranging from 0–100, according to EORTC guidelines. For the functional and global health status/quality of life scales, higher scores represent a better level of functioning. For the symptom scales, higher scores represent a greater degree of symptoms.

Patients' toxicity was graded according to the Common Terminology Criteria for Adverse Events V3.0 (CTCAE 3.0) scoring system [16]. Toxicity was assessed using questionnaires, filled out by patients at the department of radiation oncology of the University Medical Center Groningen (UMCG). The questionnaires have been previously used in a multicenter randomized phase III trial [17] and at our institute [18]. Using these questionnaires and with additional objective physician findings, such as medical interventions, the different endpoints of GI and GU toxicities were scored individually, ranging from grade 0–3 (Table 1).

Statistics

To investigate the relationship between radiation-induced toxicity and the different domains of HRQoL a Multivariate Analysis of Variance (MANOVA) was used. The main advantage of the use of a MANOVA in this study is that the multiple dependent variables over analyzing multiple dependent variables using multiple ANOVA's is that it also takes into account the inter-correlations between multiple dependent variables. Second, MANOVA has greater power than ANOVA [19], although the power of MANOVA decreases with increasing correlation [20]. Third, this multivariate approach protects against type I errors. Wilks' lambda (often referred to as the U-statistic) was used to test the impact of each prognostic factor. Wilks' lambda can take values ranging between 0, indicating large differences in group means, and 1, indicating no differences in group means.

The relationship between radiation-induced toxicity and HRQoL was analyzed by means of a two-step approach. In the first step, the impact of all GI and GU endpoints on different domains of HRQoL six months after radiotherapy was analyzed. The factors that were significantly associated with HRQoL in the first step were analyzed in a multivariate model. To investigate the robustness of the multivariate model a backwards analysis was applied using a p-value >0.05 for removal. The statistical analysis was based on a similar approach as used in a study on head and neck cancer patients by Langendijk et al. [21].

The mean scores of the HRQoL scales observed among patients with grade 1 and grade P2 toxicities were compared to those observed among patients with grade 0 toxicity at 6 months after radiotherapy. The clinical relevance of the differences in the mean scores of the HRQoL scales between groups was classified as effect sizes using Cohen's D, defined as small (0.20–0.49), moderate (0.50–0.79) and large (P>0.80) effect sizes [22,23]. To investigate whether the impact of the CTCAE late morbidity scales changed over time, differences at baseline were tested. Additionally, effect sizes at 12 and 24 months were calculated.

Results

Sample description and compliance

The majority of patients was treated with adjuvant hormonal therapy and 3D-CRT. The median age was 70 years (range 53–85). Patients' characteristics and treatment modalities are listed in Table 2. Patients' compliance on either questionnaire is listed in Table 2. Of the 224 patients who were biochemically failure free 6 months after radiotherapy, 188 patients filled out both questionnaires (84%). The compliance rate was 84% at 12 months (183 of 218 patients BFF) and 83% at 24 months (177 of 213 patients BFF).

Table 2: Patients characteristics

		Number of patients	%
Age			
	≤ 70 years	116	51
	>70 years	111	49
Tumor classification			
	T1	85	37
	T2	68	30
	T3	74	33
PSA			
	< 10	50	22
	10-20	97	43
	20-40	60	26
	>40	20	9
Adjuvant treatment			
	RT only	71	31
	RT and adjuvant hormonal therapy	156	69
Radiotherapy Modality			
	IMRT: 78 Gy	70	31
	3D-CRT: 70 Gy	157	69
Compliance Toxicity assessment			
	Baseline	222	98
	6 months after RT	200	89
	12 months after RT	184	84
	24 months after RT	187	88
Compliance HRQoL assessment			
	Baseline	221	97
	6 months after RT	209	92
	12 months after RT	207	95
	24 months after RT	203	95

Table 3: Multivariate Analysis of Variance testing the overall effect of CTCAE toxicity gradings and prognostic factors on the six EORTC QLQ-C30 scales.

Independent variables	One factor model [1]				Multi- factor model [2]	
	Wilks' Lambda	F	Degrees of Freedom	p-value	Wilks' Lambda	p-value
CTCAE late toxicity						
$CTCAE_{urinary\ incontinence}$ (grade 0 vs. 1 vs. 2-3)	0.857	2.174	12	0.013	0.861	0.019
$CTCAE_{hematuria}$ (grade 0 vs. 1 vs. 2-3)	0.917	1.202	12	ns	0.966	ns
$CTCAE_{dysuria}$ (grade 0 vs. 1 vs. 2-3)	0.885	1.705	12	ns	0.925	ns
$CTCAE_{urinary\ frequency}$ (grade 0 vs. 1 vs. 2-3)	0.970	0.342	12	ns	0.971	ns
$CTCAE_{nycturia}$ (grade 0 vs. 1 vs. 2-3)	0.938	0.799	12	ns	0.954	ns
$CTCAE_{fecal\ incontinence}$ (grade 0 vs. 1 vs. 2-3)	0.908	1.338	12	ns	0.895	ns
$CTCAE_{rectal\ bleeding}$ (grade 0 vs. 1 vs. 2-3)	0.894	1.542	12	ns	0.933	ns
$CTCAE_{rectal\ pain/cramps}$ (grade 0 vs. 1 vs. 2-3)	0.865	2.028	12	0.022	0.869	0.029
$CTCAE_{stool\ frequency}$ (grade 0 vs. 1 vs. 2-3)	0.967	0.414	12	ns	0.970	ns
Other variables						
Age (≤ 70 years vs. > 70 years)	0.982	0.514	6	ns	0.966	ns
Adjuvant therapy (RT only vs. RT and adjuvant hormonal therapy)	0.948	1.498	6	ns	0.991	ns
Treatment modality (3D-CRT vs. IMRT)	0.932	1.231	6	ns	1.142	ns

Abbreviations: RT = radiotherapy; ns = not significant.

[1] The one factor model refers to the analysis in which only one independent variable was entered in the model.

[2] The multi-factor model refers to the analysis in which initially all mentioned factors were entered as independent variables in the model (backward exclusion).

Table 4: Results of the analysis of the relationship between the CTCAE toxicity scales and the observed scores of the individual EORTC QLQ-C30 scales at 6 months after completion of radiotherapy and the clinical relevance of the observed differences.

Toxicity scale and QoL scales	Mean scores by toxicity grading							P-value **
	Grade 0	Grade 1			Grade 2-3			
		Mean	Cohen's D *	CR **	Mean	Cohen's D *	CR **	
CTCAE urinary incontinence								
Number of patients	n=126		n=34			n=11		
Global quality of life	79.0 (15.4)	72.5 (17.8)	0.39	S	65.2 (24.4)	0.70	M	p=0.012
Physical functioning	91.3 (11.2)	84.8 (13.4)	0.53	M	83.6 (6.9)	0.85		p=0.006
Role functioning	83.3 (23.9)	73.5 (26.6)	0.39	S	75.8 (26.2)	0.30	S	p=0.163
Emotional functioning	90.0 (14.9)	83.3 (19.2)	0.39	S	76.5 (27.6)	0.64	M	p=0.013
Social functioning	92.5 (15.1)	81.9 (24.1)	0.54	M	83.3 (24.7)	0.46	S	p=0.009
Fatigue	19.8 (22.4)	27.5 (25.8)	0.32	S	28.3 (24.0)	0.37	S	p=0.261
CTCAE rectal pain/cramps								
Number of patients	n=140		n=20			n=10		
Global quality of life	78.7 (16.2)	69.2 (18.4)	0.55	M	68.3 (19.6)	0.58	M	p=0.017
Physical functioning	89.6 (12.2)	91.3 (9.5)	0.16	no	86.7 (8.3)	0.29	S	p=0.562
Role functioning	82.4 (24.0)	77.5 (26.6)	0.19	no	68.3 (31.9)	0.50	M	p=0.267
Emotional functioning	89.4 (16.3)	79.5 (22.2)	0.51	M	82.5 (16.4)	0.42	S	p=0.044
Social functioning	91.5 (17.1)	85.0 (21.6)	0.34	M	73.3 (21.1)	0.95		p=0.011
Fatigue	19.4 (21.6)	31.1 (26.9)	0.48	M	34.4 (32.1)	0.56	M	p=0.032

* Cohen's D was calculated relative to Grade 0.

** CR = Classification of the clinical relevance based on Cohen's D: "no" = no clinical relevance; "S" = "small" (light grey) reference to grade 0; "M" = "moderate" (dark grey) reference to grade 0; "L" = "large" (black) reference to grade 0 (Middel et al. 2001 [21])

Between brackets: Standard deviation

Note: only the CTCAE scales that were significantly associated with the HQoL scales (Table 2) are mentioned

Association between toxicity endpoints and HRQOL

In the first analysis, a one-factor model was setup for all candidate variables at 6 months after radiotherapy (Table 3). The candidate prognostic factors included all GI and GU toxicity endpoints, patient characteristics and treatment modalities. The dependent variables in this analysis consisted of the overall quality of life, the four functioning scales and the symptom scale fatigue. Significant associations were found between HRQoL and the toxicity endpoints urinary incontinence and rectal pain/painful cramps.

In the multifactor model, only the significant variables from the one-factor model were entered into the multivariate model. To investigate the robustness of this model, a multivariate backward analysis was performed. In this analysis, all factors were entered into the model simultaneously and were backwards excluded. The multi-factor model showed, identical to the one-factor model, no effect of radiotherapy technique, hormonal treatment (yes vs. no) and patient characteristics. Two toxicity endpoints significantly affected patients' HRQoL; urinary incontinence and rectal pain/painful cramps. No significant pre-treatment differences in HRQoL were found between the toxicity groups.

Urinary incontinence and HRQoL outcome

Table 4 summarizes the means of the toxicity endpoints that had a significant impact on HRQoL. Effect sizes were calculated comparing grade 1 vs. grade 0 and grade 2–3 vs. grade 0 using Cohen's D. Urinary incontinence had an impact on all of the HRQoL scales. Comparing grade 0 with 1, small and moderate effect sizes were noted for the HRQoL scales. In particular, urinary incontinence had a marked impact on social functioning. The differences between grade 0 and grade 2–3 patients ranged from small to large. Physical functioning and global quality of life were particularly affected by urinary incontinence (effect size >0.70).

Rectal pain/painful cramping and HRQoL outcome

Rectal pain and painful cramping had a major impact on HRQoL. In relation to patients with grade 0, a moderate effect was observed for grade 1 regarding global quality of life. Large effect sizes were noted for patients with grade 2–3 as compared to patients with grade 0, especially for social functioning (Cohen's D >0.85). Small to moderate effect sizes were observed for the other HRQoL scales.

Changes over time: urinary incontinence

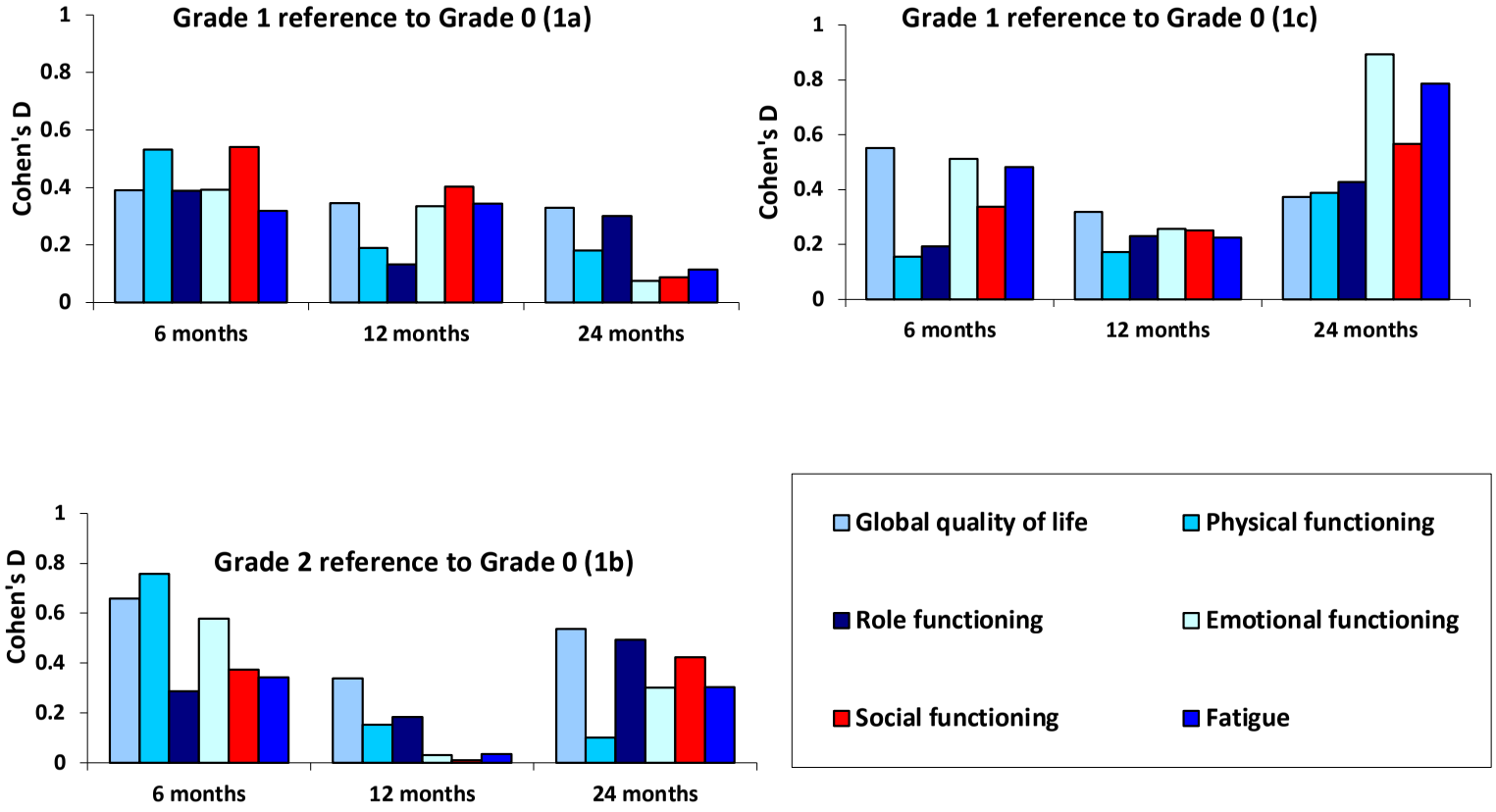
The prevalence of occasional and spontaneous urinary incontinence remained stable over the three follow-up time points, i.e. 20%, 20%, 21% (grade 1) and 6%, 7% and 8% (grade 2). Effect sizes of urinary incontinence over time are depicted in Fig. 1a and b. Fig. 1a shows the differences in effect sizes over time between grade 0 and grade 1 patients. The magnitude of the effect sizes decreased over time. The highest effect sizes were noted at 6 months after radiotherapy. Fig. 1b shows the differences in effect sizes over time between grade 0 and grade 2–3 patients. Generally speaking, the effect sizes decreased at 12 months but increased again at 24 months after radiotherapy.

Changes over time: rectal pain/painful cramping

The total number of patients with any level of rectal discomfort (both mild and moderate) remained stable over time, covering 18% of patients on all three time points. However, the prevalence of moderate discomfort decreased over time, 6%, 2% and 2%, respectively. As time progressed more patients

were observed with mild pain, 12%, 16% and 6%, respectively. Effect sizes of rectal pain/painful cramping over time are depicted in Fig. 1c. Because of the low incidence (only 4 cases) of grade 2 rectal discomfort, no effect sizes could be calculated for this group. The effect sizes comparing grade 1 with grade 0 decreased 12 months after radiotherapy and increased again 24 months after radiotherapy.

Figure 1: Effect sizes of grade 1 CTCAE$_{\text{urinary incontinence}}$ reference to grade 0 (1a),grade 2 CTCAE$_{\text{urinary incontinence}}$ reference to grade 0 (1b) and grade 1 CTCAE$_{\text{rectal pain}}$ reference to Grade 0 (1c) on HRQoL as expressed by Cohen's D as a function of time.



Discussion

The primary objective of this study was to investigate the impact of radiation-induced toxicity on HRQoL. To our knowledge this is the first study that shows that HRQoL is significantly affected by two specific treatment-related symptoms; urinary incontinence and rectal discomfort. Remarkably, a toxicity grading as low as grade 1 affects patients' HRQoL.

The results of this study are in line with research by Bacon, who showed a general impact of urinary and bowel complaints on quality of life [10]. We found, more specifically, that urinary incontinence and rectal discomfort is a cause for this depressed HRQoL. In a comparable study, Lilleby showed a univariate significant impact of urinary incontinence and bowel complaints on HRQoL [9]. However, this impact could not be confirmed in their multivariate analysis. In the current study, the functioning scales were regarded as intercorrelating dependent variables in a MANOVA design. In addition, we used undichotomized HRQoL scores, giving the opportunity to increase statistical power. The optimization of the power to show an effect was necessary because the prevalences of toxicity were relatively low and could therefore dilute HRQoL scores of patients. Despite the low prevalences, a significant and clinically relevant effect of urinary incontinence and rectal discomfort was observed on both a univariate and multivariate level. Low prevalences did affect the power to show an impact of fecal incontinence on HRQoL. Fecal incontinence was observed in only 7 patients, which was too low to reliably investigate the association between fecal incontinence and HRQoL.

The impact of urinary incontinence on HRQoL and possible clinical consequences

Urinary incontinence had a major impact on HRQoL, especially on global quality of life, physical functioning, emotional functioning and fatigue. However, the negative impact on HRQoL decreased over time. This decrease is in accordance with the findings of Sanda et al., who investigated patients' complaints using the Expanded Prostate Cancer Index Composite (EPIC-26) [24]. In that study, urinary incontinence worsened only temporarily. Remarkably, in the present study, the prevalence of urinary incontinence remained stable over time, whereas the impact of urinary incontinence on HRQoL decreased. This might indicate that patients develop effective coping strategies or change their internal standards, values and conceptualization of quality of life, known in HRQoL literature as response shift [25].

New radiation delivery techniques, such as image-guided radiotherapy (IGRT) or proton therapy may contribute to a reduction of the risks on radiation-induced side effects and subsequently to higher levels of HRQoL after treatment. In order to prevent radiation-induced side effects, it is essential to know the relationship between radiation dose distribution in adjacent organs at risk and the risk on a given side effect using normal tissue complication probability (NTCP) models. A systematic review on dose–volume effect relationships showed that, in general, dose-escalation increases GU toxicity, resulting from an unavoidable increase of dose to the caudal part of the bladder [26]. Heemsbergen et al. [27] showed that dose hot-spots in the trigonum region of the bladder may contribute to urinary obstruction. However, no conclusive data are available in current literature on a possible relationship between the dose to specific parts of the urinary tract and urinary incontinence. In order to prevent a decline in HRQol after radiotherapy as a result of urinary incontinence, this relationship should be addressed in future investigations.

The impact of rectal discomfort on HRQoL and possible clinical consequences

The incidence of rectal pain in the present study may seem high compared to a study by Fonteyne et al. [28]. However, another study by Pinkawa [29] showed higher incidences of rectal pain. The incidence depends strongly on the definition of rectal pain. In the present study, rectal pain covered questions on painful cramping, pain during defecation and painful urgency. Rectal pain may be regarded as a symptom of radiation proctitis, which leads to a loss of distensibility of the rectum or rectal structuring [30]. Other signs and symptoms of radiation proctitis include rectal bleeding, increased stool frequency and fecal incontinence. A number of authors reported on the relationship between the dose to the anorectal or anal wall and the incidence of radiation proctitis symptoms [31–34]. Also, research by Nguyen showed that $V60_{anterialwall}$ was associated with a decrease in gastro-intestinal HRQoL [35]. However, no evidence exists on the relationship between the dose to specific anatomical regions and rectal pain or painful cramping. From this point of view, it remains uncertain if the clinical introduction of new radiation techniques aiming at reducing the dose to specific anatomical structures will also results in a reduction of rectal pain and eventually in better HRQoL. To investigate the uncertainties surrounding the concept of radiation proctitis the new EORTC proctitis module, including items regarding pain and painful cramping [36], offers an opportunity to look at this toxicity more closely.

The impact of other prognostic factors on HRQoL and possible clinical consequences

In the present study, no effect of radiation technique (3D-CRT versus IMRT) and hormonal therapy (yes versus no) on HRQoL was observed. Similar results were found by Lips et al. [37]: IMRT provides a possibility to increase the radiation dose to the PTV, without deteriorating HRQoL. In the same study, hormonal therapy did not influence HRQoL as measured with the EORTC QLQ-C30. Although hormonal therapy did not have a significant influence on global quality of life, influence on sexual HRQoL scales are evident [38,39]. Lips et al. [40] showed a decrease in sexual activity after radiotherapy and literature shows an increase in erectile dysfunction after radiotherapy [41,42]. Kyrdalen [43] found that poor sexual drive was significantly associated with a low HRQoL, whereas erectile dysfunction and medication to counter erectile dysfunction were not.

Most studies reporting on NTCP models in prostate cancer focus on rectal bleeding [1–7]. Although we could not find a significant association between rectal bleeding and HRQoL, this result should be interpreted with some caution. Most of the rectal bleeding we encountered in our data was classified as grade 1. Apparently, this grading does not influence HRQoL. However, it could be assumed that patients with more severe rectal bleeding, including temporarily blood loss or the need to undergo interventions such as laser coagulation or hyperbaric oxygen, do experience a worsening in HRQoL.

Although our results show a decrease in HRQoL after radiotherapy due to side effects, only a relatively small number of patients actually experience these side effects, possibly diluting our results. Therefore, we cannot be totally conclusive about the explanation of a decrease in HRQoL after radiotherapy. Also, our group was relatively heterogeneous, considering different radiotherapy treatment modalities and considering different adjuvant hormonal therapy options. Although these variables did not influence HRQoL in our study, additional research with a more homogeneous patient group is needed to ascertain these results.

The focus of the current study was on general domains of HRQoL. It may well be important to analyze the impact of other treatment related symptoms by means of the QLQ-PR25 [44]. However, it should be taken into account that radiation induced toxicity as can be derived from the QLQ-PR25 is singly patient-rated, whereas the CTCAE toxicity endpoints used in our study offered the opportunity to investigate the impact of possible clinical interventions, that are not included in the QLQ-PR25.

In order to categorize clinically meaningful changes Cohen's effect sizes were used in the current study. Another method to analyse clinically meaningful changes is Osoba's 10 point difference [45]. The criteria from Osoba are based on research on patients with either breast cancer or small-cell lung cancer. As prostate cancer patients may experience their functioning in daily life after radiotherapy differently, we argue that the meaning of clinically important differences in health related quality of life may also be different. Therefore we choose to use the statistical criteria as proposed by Cohen that are more universal and do less depend on the patient group analyzed.

Conclusion

Urinary incontinence and rectal discomfort have an invalidating impact on prostate cancer patients' HRQoL after radiotherapy. Current studies on prostate cancer radiotherapy focus mainly on severe toxicity (grade P2), whereas even slight toxicity affects a patient's HRQoL. The impact of severe rectal bleeding on a patient's HRQoL may be obvious, but also more temporary as compared to the persisting impact of urinary incontinence and rectal discomfort.

References

[1] Cheung R, Tucker S, Ye J, et al. Characterization of rectal normal tissue complication probability after high-dose external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2004;58:1513–9.
[2] Peeters S, Hoogeman M, Heemsbergen W, et al. Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: normal tissue complication probability modeling. Int J Radiat Oncol Biol Phys 2006;66:11–9.
[3] Defraene G, Van den Bergh L, Al-Mamgani A, et al. The benefits of including clinical factors in rectal normal tissue complication probability modeling after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2011;82:1233–42.
[4] Peeters S, Lebesque J, Heemsbergen W, et al. Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2006;64:1151–61.
[5] Coyne KS, Zhou Z, Thompson C, et al. The impact on health-related quality of life of stress, urge and mixed urinary incontinence. BJU Int 2003;92:731–5.
[6] Lips I, Dehnad H, Kruger A, et al. Health-related quality of life in patients with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs. 70 Gy conformal radiotherapy in a prospective and longitudinal study. Int J Radiat Oncol Biol Phys 2007;69:656–61.
[7] Ferrer M, Suárez J, Guedea F, et al. Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;72:421–32.
[8] Beckendorf V, Guerif S, Prisé Le, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2010;80:1056–63.
[9] Lilleby W, Fossa SD, Waehre HR, et al. Long term morbidity and quality of life in patients with localized prostate cancer undergoing definitive radiotherapy or radical prostatectomy. Int J Radiat Oncol Biol Phys 1999;43:735–43.
[10] Bacon CG, Giovannucci E, Testa M, et al. The association of treatment-related symptoms with quality-of-life outcomes for localized prostate carcinoma patients. Cancer 2002;94:862–71.
[11] Lev EL, Eller LS, Gejerman G, et al. Quality of life of men treated with brachytherapies for prostate cancer. Health Qual Life Outcomes 2004;11:1–11.
[12] Bolla M, de Reijke T. Long term adjuvant hormonal treatment with LHRH analogue versus no further treatment in locally advanced prostatic carcinoma treated by external irradiation and six months combined androgen blockage—a phase III study. EORTC Trial 22961. A joint trial of the EORTC Radiotherapy and EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC DATA CENTER, Brussels, 1997.
[13] Bolla M. EORTC Radiotherapy Cooperative Group, three dimensional conformal radiotherapy alone vs three dimensional conformal therapy plus adjuvant hormonal therapy in localized T1b-c, T2a, N0, M0 prostatic carcinoma. A Phase III Randomized Study. EORTC PROTOCOL 22991. Brussels, 2000.
[14] Bel A, van Herk M, Bartelink H, et al. A verification procedure to improve patient set-up accuracy using portal images. Radiother Oncol 1993;29:253–60.
[15] Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Nation Cancer Instit 1993;85:365–76.
[16] Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176–81.
[17] Peeters STH, Heemsbergen WD, van Putten WLJ, et al. Acute and late complications after radiotherapy for prostate cancer: results of a multicentre randomized trial comparing 68 Gy to 78 Gy. Int J Radiat Oncol Biol Phys 2005;61:1019–34.

[18] van der Laan HP, van den Bergh A, Schilstra C, et al. Grading-systemdependent volume effects for late radiation-induced rectal toxicity after curative radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1138–45.
[19] Huberty CJ, Morris JD. Multivariate analysis versus multiple univariate analysis. Psychol Bull 1989;105:302–8.
[20] Ramsey PH. Empirical power of procedures for comparing two groups on p variables. J Educat Statist 1982;7:139–56.
[21] Langendijk JA, Doornaert P, Leeuw Verdonck-de, et al. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol 2008;26:3770–6.
[22] Middel B, Stewart R, Bouma J, et al. How to validate clinically important change in health-related funcional status: is the magnitude of the effect size consistently related to magnitude of change as indicated by a global question rating? J Eval Clin Pract 2001;7:399–410.
[23] Cohen D. Statistical power analysis for the behavioural sciences. 2nd ed. Hillsdale (NJ): Erlbaum; 2007.
[24] Sanda MG, Michalski Dunn RL, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008;358:1250–61.
[25] Schwartz CE, Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med 1999;48:1531–48.
[26] Fiorino C, Valdagni R, Rancati T, et al. Dose–volume effects for normal tissues in external radiotherapy: pelvis. Radiother Oncol 2009;93:153–67.
[27] Heemsbergen WD, Al-Mamgani A, Witte MG, et al. Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): relationships with local dose, acute effects, and baseline characteristics. Int J Radiat Oncol Biol Phys 2010;78:19–25.
[28] Fonteyne V, De Neve W, Villeirs G, et al. Late radiotherapy-induced lower intestinal toxicity (RILIT) of intensity-modulated radiotherapy for prostate cancer: the need for adapting toxicity scales and the appearance of the sigmoid colon as co-responsible organ for lower intestinal toxicity. Radiother Oncol 2007;84:156–63.
[29] Pinkawa M, Piroth MD, Fischedick K, et al. Self-assessed bowel toxicity after external beam radiotherapy for prostate cancer-predictive factors on irritative symptoms, incontinence and rectal bleeding. Radiat Oncol 2009;4:36.
[30] Leiper K, Morris AI, et al. Treatment of radiation proctitis. J Clin Oncol 2007;19:724–9.
[31] Gulliford S, Partridge M, Sydes MR, et al. Parameters for the Lyman Kutcher Burman (LKB) model of Normal Tissue Complication Probability (NTCP) for specific rectal complications observed in clinical practise. Int J Radiat Oncol Biol Phys 2011;102:347–51.

Chapter 4: Normal tissue complication probability (NTCP) models for late rectal bleeding, stool frequency and fecal incontinence after radiotherapy in prostate cancer patients.

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Abstract

Background and purpose
Curative radiotherapy for prostate cancer may lead to anorectal side effects, including rectal bleeding, fecal incontinence, increased stool frequency and rectal pain. The main objective of this study was to develop multivariable NTCP models for these side effects.

Material and methods
The study sample was composed of 262 patients with localized or locally advanced prostate cancer (stage T1–3). Anorectal toxicity was prospectively assessed using a standardized follow-up program. Different anatomical subregions within and around the anorectum were delineated. A LASSO logistic regression analysis was used to analyze dose volume effects on toxicity.

Results
In the univariable analysis, rectal bleeding, increase in stool frequency and fecal incontinence were significantly associated with a large number of dosimetric parameters. The collinearity between these predictors was high (VIF > 5). In the multivariable model, rectal bleeding was associated with the anorectum (V70) and anticoagulant use, fecal incontinence was associated with the external sphincter (V15) and the iliococcygeal muscle (V55). Finally, increase in stool frequency was associated with the iliococcygeal muscle (V45) and the levator ani (V40). No significant associations were found for rectal pain.

Conclusions
Different anorectal side effects are associated with different anatomical substructures within and around the anorectum. The dosimetric variables associated with these side effects can be used to optimize radiotherapy treatment planning aiming at prevention of specific side effects and to estimate the benefit of new radiation technologies.

Introduction

Dose escalation in external beam radiotherapy results in increased biochemical tumor control for localized prostate cancer [1]. However, higher dose to adjacent normal tissues may lead to increased rates of moderate to severe side effects such as rectal bleeding, fecal incontinence, increased stool frequency and rectal pain. As a consequence, patients may experience decreased quality of life [2,3].

In order to reduce the risk of late anorectal side effects by optimizing radiation dose distributions, information on the relation between complication risk and dose-volume parameters is crucial. Currently, a large number of studies have shown relations between dose to anatomical regions and late anorectal side effects described by normal tissue complication probability (NTCP) models [4–8]. The majority of NTCP studies related the dose to the entire anorectum as single organ at risk (OAR) for rectal bleeding, increased stool frequency, and fecal incontinence. As the pathophysiology of these side effects is different [9], the question arises as to whether dose distributions in more specific anatomical substructures within or around the anorectum are more relevant.

Currently no multivariable models exist on dose to more specific anatomical regions and late side effects. Therefore, the main objective of this study was to develop multivariable NTCP models for rectal bleeding, incontinence, stool frequency and rectal pain taking into account dose distributions to several anatomical substructures and other candidate prognostic factors.

Methods

Patients

The population of this prospective cohort study was composed of 262 patients with prostate cancer confined to the prostatic capsule (stage T1–3). All patients were treated with external beam radiotherapy at the University Medical Center Groningen (UMCG) between 2005 and 2009. The minimal follow up of patients alive was 3 years. Radiotherapy was delivered with linear accelerators using 6 MV photons with intensity modulated radiotherapy (IMRT). Patients were treated 5 times a week, 2 Gy daily, to a total dose of 78 Gy on the prostate. Setup accuracy was verified during delivery by matching bony anatomy or implanted fiducial markers. Most patients with locally advanced prostate cancer received adjuvant hormonal treatment (Table 1). For the purpose of the current analysis, only patients biochemically failure free at three years after treatment were eligible for this study. Additionally, two patients were excluded from the final analysis; one patient developed a severe stroke and one patient developed bladder carcinoma after radiotherapy.

Table 1: Patient and treatment characteristics

		Number of patients	%
Age			
	≤ 70 years	151	58
	>70 years	111	42
Tumor classification			
	T1	102	39
	T2	114	44
	T3	46	18
PSA			
	< 4	9	3
	4-10	82	31
	>10	171	65
Gleason			
	5-6	95	36
	7	106	41
	8-10	61	23
Treatment related factors			
	Hormonal therapy	113	43
	Fiducial markers	80	31
Pre-treatment related factors			
	History of diabetes	32	12
	Smoking (15 missing)	100	38
	History of cardiovascular disease	86	33
	History of abdominal surgery	92	35
	Anticoagulants use	92	35

Target delineation

Two clinical target volumes (CTV) were defined, one for the prostate and one for the seminal vesicles. Each CTV was expanded 10 mm in three dimensions to obtain the corresponding planning target volumes (PTV), using the automatic expansion algorithm of the treatment-planning system.

Organ at risk delineation

The cranial border of the anorectum was defined at the location where the rectum turned horizontally into the sigmoid colon but not superior to the caudal border of the sacroiliac joint. The caudal border of the rectum was defined to include the anus but not lower than the inferior border of the ischial tuberosity. The anorectum was divided into two sections: the anal canal, corresponding to the inferior part (ischial tuberosity to 3 cm superior) and the rectum, corresponding to the remaining superior part (Fig. 1a). The anal and rectal walls were defined as the outermost 3 mm of the anal canal and rectum (Fig. 1b and c). Subsequently, the anal and rectal structures were divided into an anterior and a posterior part.

The pelvic floor muscles were delineated as described by Smeenk et al. [10]. The internal anal sphincter (IAS) was defined as the distal extension of the smooth muscle layer of the anorectum (Fig. 2). The external anal sphincter (EAS) encircles the internal sphincter. The puborectal muscle (PRM) is a U-shaped muscle connecting to the pubic bone. The cranial extension is defined as the Iliococcygeus muscle (ICM). The PRM and ICM together form the levator ani (LA) muscle.

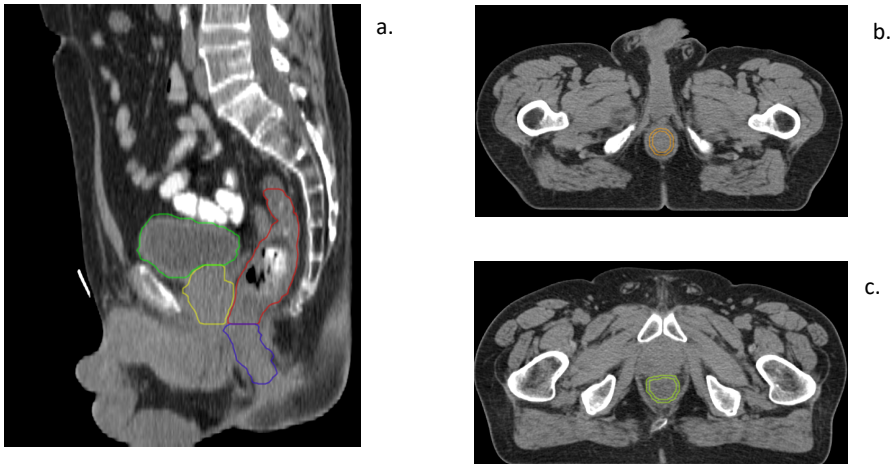

Figure 1 a. Sagittal view of bladder (green), prostate (yellow), anal canal (purple), rectum (red).
b. Transverse view of the anal wall
c. Transverse view of the rectal wall

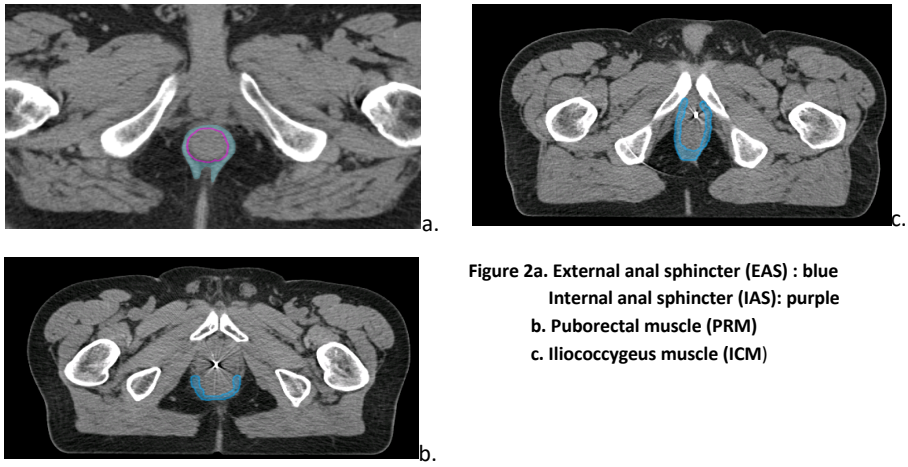

Figure 2a. External anal sphincter (EAS) : blue
Internal anal sphincter (IAS): purple
b. Puborectal muscle (PRM)
c. Iliococcygeus muscle (ICM)

Endpoints

Side effects were assessed prospectively using questionnaires, filled out by patients at the department of Radiation Oncology, UMCG. The questionnaires have been previously used in a multicenter randomized phase III trial [11] and at our institute [12]. Using these questionnaires and additional objective data on medical interventions, such as the prescription of medication, the different endpoints were scored according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE 3.0) scoring system [13], finally resulting in a single score per endpoint for the incidence of toxicity over the follow-up interval. The minimal follow up of patients alive was 3 years.

Rectal bleeding was defined as daily loss of blood, requiring one or more laser coagulation (CTCAE grade≥2), fecal incontinence was defined as the unwilling loss of stool (CTCAE grade≥2), stool frequency was defined as an increase of more than three times per day compared to baseline (CTCAE grade≥2) and rectal pain was defined as severe pain during defecation (CTCAE grade≥2).

Statistical analysis

The candidate dosimetric predictors of the four endpoints in our analysis were selected based on available literature on both prostate NTCP modeling [4,10] and on pathophysiology of late rectal dysfunction [9] and included the mean dose for each organ at risk and the relative volumes receiving 5–70 Gy, in 5 Gy bins (V5–V70). Additionally, equivalent uniform dose (EUD) parameters with n ranging from 0.05 to 0.5 were included into the model [14,15]. Finally, we included age, adjuvant hormonal treatment, and pretreatment factors (Table 1), which were retrieved retrospectively from the patient charts, as candidate predictors. Patients with missing data in the candidate dataset were removed from the analysis.

To develop a prediction model for each endpoint, a univariable logistic regression analysis was performed first to show the crude effect of each candidate variable on every endpoint. For the development of the multivariable prediction models the least absolute shrinkage and selection operator (LASSO) method was used, which is a logistic regression analysis with a penalty for the magnitude of the regression coefficients to prevent overfitting. The optimal penalty value was determined using cross-validation. Because of the high collinearity of the candidate predictors, the set of variables was further reduced prior to the LASSO analysis, until the variance inflation factor (VIF) was smaller than 5. First, (if VIF > 5) all variables with univariable associations with $p > 0.157$ (Wald test) were removed. Subsequently, (if still VIF > 5) the set of dosimetric variables was reduced, such that for each structure (or set of overlapping structures) only the strongest predictor remained (as measured by the likelihood of the corresponding univariable model). Finally, if multivariable analysis resulted in a negative coefficient for a dosimetric variable, that variable was removed from the analysis.

Model performance was described using various validation measures [16,17]. The discriminating ability of the model was described by the Area Under the receiver operating characteristic curve (AUC). The discrimination slope was calculated as the absolute difference between the mean predicted NTCP value for patients with and without the outcome. Nagelkerke's R2 was calculated as a pseudo measure of explained variance. Finally, the gain and intercept of the model calibration were calculated, and the calibration was evaluated using a Hosmer–Lemeshow test with 10 equal groups [18]. The model performance was internally validated and corrected for optimism with regular bootstrapping [19]. Results with $p < 0.05$ were considered as significant. Associations with $p > 0.157$ were considered as unobserved.

Results

Twelve out of 256 patients (4.7%) experienced grade 2 or higher rectal bleeding. The candidate predictors of severe rectal bleeding included dosimetric predictors of all anorectal (sub)structures and pre-treatment variables diabetes, age, cardiovascular disease, abdominal surgery, anticoagulants use and adjuvant hormonal treatment. In the univariable analysis the V50-V70, different EUD's and mean dose for anorectum, rectum, rectal wall, rectum-posterior and rectum-anterior were associated with rectal bleeding (Table 2). In addition, a borderline significant relationship was found with cardiovascular disease and anticoagulants use. No association was observed between rectal bleeding and the other pre-treatment related factors (Table 1). Because of high collinearity among the predictors (VIF >5), the set of candidate variables was reduced prior to the multivariable LASSO analysis. Also, because all patients that used anticoagulants had a history of cardiovascular disease, the latter variable was dropped. In the final model, the volume of the anorectum receiving ≥70 Gy (anorectum(V70)) and the use of anticoagulants predicted rectal bleeding with a corrected AUC of 0.88 (CI: 0.78-0.97; see all measures in table 3). In individual cases, the risk of rectal bleeding can be estimated using the following equation:

$$\text{NTCP} = \frac{1}{(1+ e^{-S})}$$

Where S is defined as:

$$S = -8.09 + 0.32 \cdot (\text{anorectum (V70)}) + 1.19 \cdot (\text{anticoagulant use})$$

with anorectum(V70) in relative volume % and anticoagulant use is 1 (yes) or 0 (no).

The Hosmer-Lemeshow test was not significant (chi square 9.85; df 8; p=0.28), indicating good agreement between expected and observed complication rates (Figure 3a).

In total, 20 out of 256 patients experienced fecal incontinence (7.8%). The candidate predictors of fecal incontinence included dosimetric predictors of all anorectal (sub)structures and all pelvic floor muscles. In the univariable analysis low, intermediate and high dose and different EUD's of the internal anal sphincter, external anal sphincter, iliococcygeal muscle and levator ani muscle were associated with fecal incontinence (Table 2). The variance inflation factor showed high collinearity (VIF > 5) among the predictors, and the number of dosimetric variables was therefore reduced prior to multivariable analysis. The internal sphincter was excluded because this variable resulted in a model with a negative dosimetric coefficient. The LASSO analysis resulted in a model with two predictors, including the volume of the external sphincter receiving ≥ 15 Gy and the volume of the iliococcygeal muscle receiving ≥ 55 Gy, with a corrected AUC of 0.85 (CI: 0.76- 0.94; see all measures in table 3). In individual cases, the risk of fecal incontinence can be estimated using the following equation:

$$\text{NTCP} = \frac{1}{(1+ e^{-S})}$$

Where S is defined as:

Table 2: Univariable logistic regression analysis for rectal bleeding, stool frequency and fecal incontinence

		Odds ratio*,**	p-Value**
Rectal bleeding ≥ grade 2 (n=12)			
Cardiovascular disease		2.87	0.079
Anticoagulants use		3.00	0.065
Anorectum	mean dose	1.11	0.105
	V50-V70	1.05-1.58	<0.001 - 0.068
	EUD (0.05-0.50)	1.29-2.91	<0.001 - 0.008
Rectalwall	V50-V70	1.05-1.20	<0.001 - 0.042
	EUD (0.05-0.50)	1.17-2.41	<0.001 - 0.033
Rectum	V50-V70	1.04-1.38	<0.001 - 0.051
	EUD(0.05-0.50)	1.24-2.65	<0.001 - 0.013
Rectum-posterior	V50-V70	1.04-1.71	<0.001 - 0.020
	EUD(0.05-0.50)	1.19-1.40	<0.001 - 0.001
Rectum-anterior	V55-V75	1.05-1.15	<0.001 - 0.046
	EUD(0.05-0.50)	1.20-2.63	<0.001 - 0.028
Fecal incontinence (n=20)			
Internal anal sphincter (IAS)	mean dose	1.09	0.023
	V10-V45	1.04-1.05	0.007-0.150
External anal sphincter (EAS)	mean dose	1.19	<0.001
	V10-V70	1.07-1.08	<0.001-0.108
	EUD(0.20-0.50)	1.15-1.19	<0.001-0.009
Iliococcygeal muscle (ICM)	mean dose	1.09	0.014
	V40-V70	1.03-1.04	0.001-0.110
	EUD(0.10-0.20)	1.08-1.10	0.028-0.029
Levator ani muscle (LAM)***	mean	1.09	0.13
	V40-V65	1.04-1.05	0.018-0.076
Increased stoolfrequency >3 (n=29)			
Iliococcygeal muscle (ICM)	mean dose	1.13	<0.001
	V25-V65	1.04-1.72	<0.001-0.120
	EUD(0.5-2)	1.15-1.16	<0.001
Puborectal muscle (PRM)	mean dose	1.07	0.077
	V25-V55	1.03-1.65	0.002-0.076
Levator ani muscle (LAM)***	mean dose	1.2	<0.001
	V25-V70	1.03-1.24	<0.001-0.070
	EUD(0.5-2)	1.20-1.26	<0.001-0.002

* For dose variables OR: increase per 1 Gy increase in dose
For volume parameters: increase per 1% increase in volume

** range is displayed when > 1 variable, only results with p<0.157 are shown

*** Levator ani muscle=Iliococcygeal muscle + Puborectal muscle

Figure 3: Final logistic regression analysis for rectal bleeding, stool frequency and fecal incontinence. The left graphs represent relative volumes with corresponding NTCP risk. The right graphs respresent calibration plots for internal validation. The black points represent the Hosmer–Lemeshow groups, the dashed line represents the identity line.

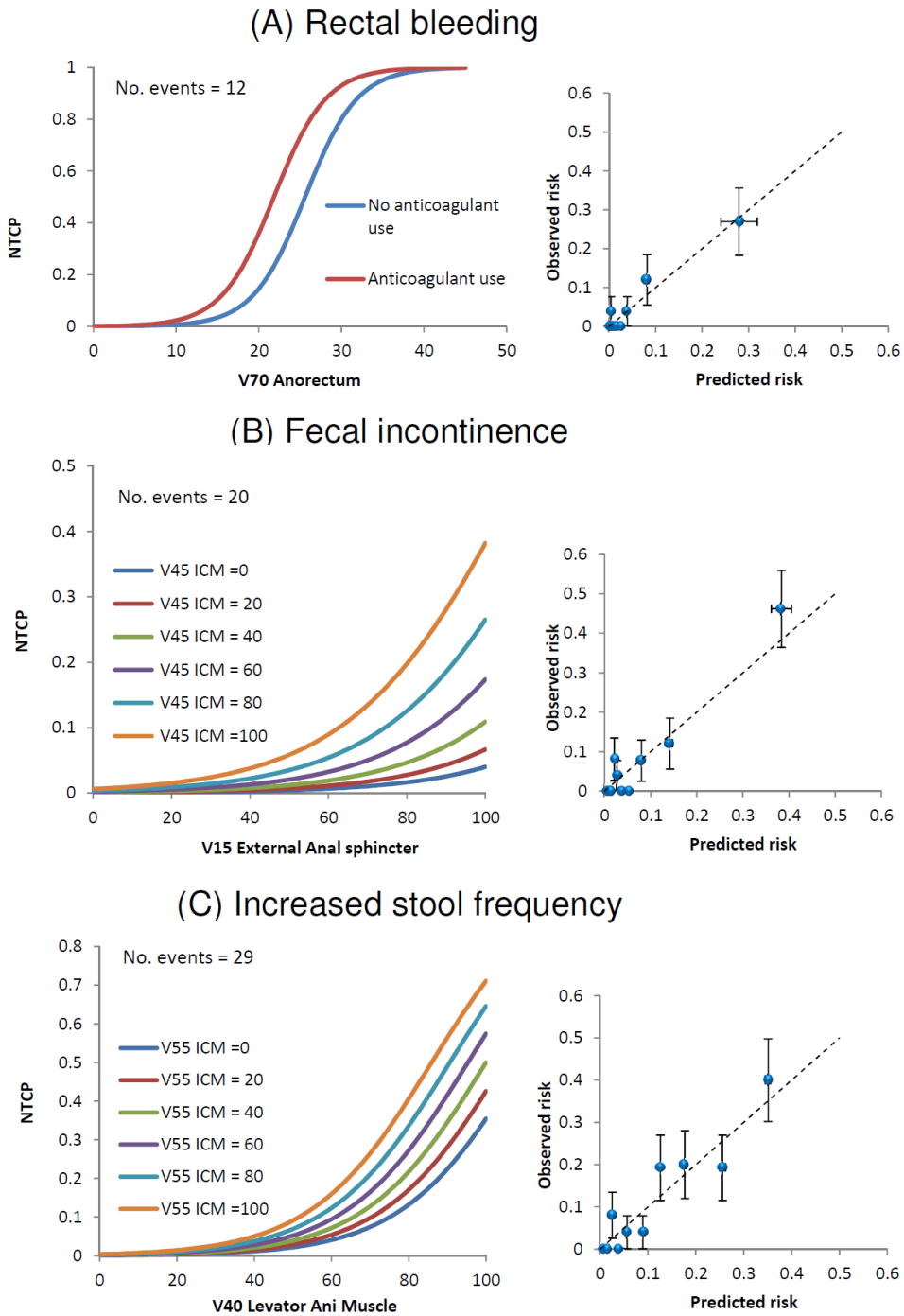

Table 3: Performance and calibration measures for the multivariable LASSO model for rectal bleeding, stool frequency and fecal incontinence. Apparent measures were calculated using the complete dataset on which the model was trained; the corrected measures were adjusted for optimism as calculated with a bootstrapping procedure, from which also the standard error was derived. Per endpoint the standard error for each predictor is displayed.

	Rectal bleeding			Fecal incontinence			Increased stoolfrequency		
Performance and calibration measure	**Apparent**	**Corrected**	**Standard error**	**Apparent**	**Corrected**	**Standard error**	**Apparent**	**Corrected**	**Standard error**
AUC*	0.89	0.88	0.05	0.86	0.85	0.05	0.80	0.79	0.03
Nagelkerkes R^2	0.39	0.33	0.10	0.32	0.27	0.09	0.23	0.20	0.06
Slope	1.09	0.99	0.17	1.08	1.02	0.09	1.08	1.02	0.13
Discrimination Slope	0.25	0.23	0.09	0.19	0.17	0.07	0.13	0.12	0.04
Regression coefficients standard error and selection frequency for each predictor									
	Intercept	**Ano-rectum**	**Anti-coagulants**	**Intercept**	**External sphincter**	**Iliococcy-geal muscle**	**Intercept**	**Illiococcy-geal muscle**	**Levator ani**
		V70	**use**		**V15**	**V55**		**V45**	**V40**
Standard error	2.06	0.11	0.90	0.033	0.014	0.013	2.62	0.012	0.037
Selection frequency	100%	100%	81%	100%	100%	89%	100%	98%	88%

* AUC: Area under the curve

$$S = -7.00 + 0.064 \cdot (\text{external sphincter(V15)}) + 0.015 \cdot (\text{iliococcygeal muscle(V55)})$$

With external sphincter(V15) and iliococcygeal muscle(V55) in relative volume %.

The Hosmer-Lemeshow test had a chi square of 7.27 (df=8, p=0.51), indicating good agreement between expected and observed complication rates (Figure 3b).

A total number of 29 out of 254 patients (11.4%) experienced an increase in stool frequency of more than 3 compared to baseline. The candidate predictors of an increase in stool frequency included dosimetric predictors of all anorectal (sub)structures and all pelvic floor muscles. In the univariable analysis the mean and intermediate dose to the iliococcygeal muscle, puborectal muscle and levator ani muscle and different EUD's were associated with increased stool frequency (Table 2). The variance inflation factor showed high collinearity (VIF > 5) among the predictors. Based on the LASSO variable selection method, the final multivariable analysis with the best model performance resulted in a model with two predictors, including the volume of the iliococcygeal muscle receiving ≥ 45 Gy and the volume of the levator ani receiving ≥ 40 Gy, with a corrected AUC of 0.79 (CI 0.72-0.86). In individual cases, the risk of increased stool frequency can be estimated using the following equation:

$$\text{NTCP} = \frac{1}{(1+ e^{-S})}$$

Where S is defined as:

$$S = -7.78 + 0.027 \cdot (\text{iliococcygeal muscle(V45)} + 0.046 \cdot (\text{levator ani muscle(V40)}$$

With iliococcygeal muscle(V45) and levator ani muscle(V40) in relative volume %.
The Hosmer-Lemeshow test was not significant (chi square 7.43; df 8; p=0.49), indicating good agreement between expected and observed complication rates (Figure 3c).

In total, 16 patients (6.1%) experienced rectal pain (≥grade 2). The candidate predictors of rectal pain included dosimetric predictors of all anorectal (sub)structures and all pelvic floor muscles. In the univariable and multivariable analysis no significant associations were found for any of the dosimetric or pre-treatment predictors with rectal pain.

Discussion

The main objective of this study was to develop multivariable NTCP models for rectal bleeding, incontinence, stool frequency and rectal pain based on pretreatment and dosimetric variables of different anatomical subregions within or around the anorectum. For three endpoints the multivariable analysis resulted in models with two highly predictive variables. Rectal bleeding was best predicted by the V70 of the anorectum and the use of anticoagulants. Incontinence was best predicted by the V15 to the external anal sphincter and the V55 of the iliococcygeal muscle. Stool frequency was best predicted by the V45 of the iliococcygeal muscle and the V40 of the levator ani muscle. No significant associations were found for rectal pain.

The association between the dose to the anorectum as a solid single organ and the complication probability has been extensively investigated in other studies [8,20,21]. Although our study included a large number of anatomical substructures within the anorectum to predict rectal bleeding, the results suggest identical constraints to the V70 of the anorectum as mentioned in a review on dose-volume effects in normal tissue [4]. In the current study the addition of dose to different anatomical substructures within the anorectum did not result in a better model for the prediction of rectal bleeding. Notably, the planned doses in the specific substructures of the anal and rectal walls were not better predictors for rectal bleeding than the dose in the larger encompassing anorectum. A possible explanation is that the actual given dose is blurred compared to the planned dose due to setup-errors and motion, and that planned dose in larger encompassing structures is more representative for the actual given dose than planned dose in small wall-like substructures. The actual given dose may be more in line with the planned dose by use of an endorectal balloon [10]. However, patients in our cohort were not treated with an endorectal balloon and therefore future research should focus on patients treated with endorectal balloons in order to further specify the anatomical substructures that are responsible for rectal bleeding.

Fransson et al. [22] observed a large difference in incontinence and stool frequency between prostate cancer patients treated with EBRT and age-matched controls. Smeenk et al. were the first to try to find an explanation for these incontinence related complaints by analyzing the relationships with the dose to different pelvic floor muscles by means of a univariable analysis [10]. The results of the univariable analysis of the current study are in line with those results, i.e., that the doses to all of the pelvic floor muscles were highly associated with incontinence. In contrast, the multivariable analysis revealed that only the dose to the iliococcygeal muscle (part of the levator ani muscle) and external sphincter were independently associated with fecal incontinence. The question may arise why specifically these structures are involved in these incontinence related complaints. The external sphincter is responsible for the voluntary movement of stool through the anus, in contrast to the internal sphincter, which is involuntary [9], and is cranially attached to the levator ani muscle. The current study shows that both the lower part (external sphincter) and upper part (iliococcygeal muscle) of the pelvic floor muscles are involved in incontinence. This is in line with [23] and results described by Dobben et al. [24], where incontinence was related to external sphincter defects, such as anal sphincter atrophy. More specifically, Yeoh [25] found that weakening of the external sphincter (and not the internal) was observed among incontinent patients and manometry testing showed progressive reduction of anal pressure among EBRT (external beam radiotherapy) treated patients due to weakening of the external sphincter. In the current study, increase in stool frequency was highly associated with the dose to different pelvic floor muscles, i.e., the levator ani muscle and, in particular, the iliococcygeal muscle. This is in agreement with a study on frequent voiding [26], in which worsening of levator ani defects was related to frequent voiding. Another study [27] showed that clinical improvement after rectal defects was associated with a strengthening of the levator ani muscle by pelvic floor exercises. These exercises may offer an additional opportunity to decrease the perseverance of rectal defects that may be caused by radiation therapy.

The iliococcygeal muscle is part of the levator ani and as a result, the correlation between these predictors was relatively high (0.79). However, both remained predictive in the multivariable model, indicating that the levator ani as a whole and particularly the iliococcygeal muscle play an essential role in continence and voiding.

Although we tried to find an explanation for rectal pain among patients treated with EBRT for prostate cancer, we were not able to find any (dosimetric) predictor for this toxicity. Several researchers have investigated this toxicity [28,29], but to our knowledge no direct relationship between dosimetric parameters and pain can be found in literature. Pain is a relatively subjective endpoint, in contrast to the other endpoints, and other individual factors such as self-efficacy, may play a role in the pain experience [30]. As pain has a direct impact on the quality of life [2], further research should focus on finding other possible predictors of rectal pain among prostate cancer patients.

The number of patients with severe (grade≥2) side effects in prostate cancer patients in our cohort is relatively small, possibly affecting the robustness of the model. The question may arise as to whether the internal validity of the models stated in this article is compromised by this low incidence. In order to address this, additional multivariable analyses with alternative methods were performed, including logistic regression with forward variable selection using the Wald test or bootstrapping [31] and reducing the variable collinearity with PCA (principal component analysis) preprocessing. These analyses all resulted in very similar models, with the same dominating factors, suggesting a relatively high stability of the associations in this dataset, independent of the method of analysis. An additional simulation analysis on these data [32] showed that, despite high collinearity and low incidence, the data driven selection used, performed relatively stable. Although highly stable in these data, we recommend to evaluate these models in external datasets.

The final models presented cover different dose predictors, i.e. cutoff values derived from a Dose Volume Histogram (DVH). A well-known limitation of using DVH cutoff values in modeling is that only one point of the DVH is considered and the rest is ignored. Use of the Equivalent Uniform Dose (EUD) may be a solution for this problem [14,15], taking into account the whole DVH. Therefore analyses using the EUD as a predictor were performed. Although the EUD models performed well in the univariable analysis, for all endpoints the previously stated models performed better in terms of likelihood and were therefore presented as the final models. Although in our data single cut-off values from the DVH had better model performance than EUD based models, confirmation in external datasets is warranted.

The results of this study provide important information on which anatomical structures in prostate cancer IMRT could be considered as organ at risk. Whether dose in these structures can be reduced using alternative plan optimization or dose delivery techniques, and whether this reduction will actually result in less side effects should be confirmed in plan comparison and prospective cohort studies.

Different anatomical subregions are associated with different anorectal side effects. Rectal bleeding is associated with high doses to the anorectum and anticoagulants use, anal incontinence is associated with low doses to external anal sphincter and iliococcygeal muscles and increase in stool frequency is associated with intermediate dose to the levator ani muscles. Although internal validation showed good results, further evaluation in independent datasets is warranted.

References

[1] Zelefsky MJ, Pei X, Chou JF, Schechter M, Kollmeier M, Cox B, et al. Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. Eur J Urol 2011;60:1133–9.
[2] Schaake W, Wiegman EM, Groot de M, Laan van der HP, Schans van der CP, Bergh van den ACM, et al. The impact of gastrointestinal and genitourinary toxicity on health related quality of life among irradiated prostate cancer patients. Radiother Oncol 2014;110:284–90.
[3] Stenmark MH, Conlon ASC, Johnson S, Daignault S, Litzenberg D, Marsh R, et al. Dose to the inferior rectum is strongly associated with patient reported bowel quality of life after radiation therapy for prostate cancer. Radiother Oncol 2014;110:291–7.
[4] Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose–volume effects for normal tissues in external radiotherapy: pelvis. Radiother Oncol 2009;93:153–67.
[5] Ebert MA, Foo K, Haworth A, Gulliford SL, Kennedy A, Joseph DJ, et al. Gastrointestinal dose-histogram effects in the context of dose-volumeconstrained prostate radiation therapy: analysis of data from the RADAR prostate radiation therapy trial. Int J Radiat Oncol Biol Phys 2014;91:595–603.
[6] Fonteyne V, Ost P, Vanpachtenbeke F, Colman R, Sadeghi S, Villeirs G, et al. Rectal toxicity after intensity modulated radiotherapy for prostate cancer: which rectal dose volume constraints should we use? Radiother Oncol 2014;113:398–403.
[7] Wortel RC, Witte MG, van der Heide UA, Pos FJ, Lebesque JV, van Herk M, et al. Dose–surface maps identifying local dose–effects for acute gastrointestinal toxicity after radiotherapy for prostate cancer. Radiother Oncol 2015;117:515–20.
[8] Peeters STH, Hoogeman MS, Heemsbergen WD, Hart AAM, Koper PCM, Lebesque JV. Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: normal tissue complication probability modeling. Int J Radiat Oncol Biol Phys 2006;66:11–9.
[9] Petersen E, Bregendahl S, Langschwager M, Laurberg S, Brock C, Drewes A, et al. Pathophysiology of late anorectal dysfunction following external beam radiotherapy for prostate cancer. Acta Oncol 2014;53:1398–404.
[10] Smeenk RJ, Hoffmann AL, Hopman WPM, Th. van Lin ENJ, Kaanders JHAM. Dose-effect relationships for individual pelvic floor muscles and anorectal complaints after prostate radiotherapy. Int J Radiat Oncol Biol Phys 2011;83:636–44.
[11] Peeters STH, Heemsbergen WD, Putten van WLJ, Slot A, Tabak H, Mens JW, et al. Acute and late complications after radiotherapy for prostate cancer: Results of a multicenter randomized trial comparing 68 Gy to 78 Gy. Int J Radiat Oncol Biol Phys 2005;61:1019–34.
[12] Laan van der HP, Bergh van den ACM, Schilstra C, Vlasman R, Meertens H, Langendijk JA. Grading-system-dependent volume effects for late radiationinduced rectal toxicity after curative radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1138–45.
[13] Trotti A, Colevas AD, Setser A, Rusch V, Jaquesc D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176–81.
[14] Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. Med Phys 1997;24:103–10.
[15] Tomatis S, Rancati T, Fiorino C, Vavassori V, Fellin G, Cagna E, et al. Late rectal bleeding after 3D-CRT for prostate cancer: development of a neural-networkbased predictive model. Phys Med Biol 2012;57:1399–412.
[16] Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. Epidemiology 2010;21:128–38.
[17] Vergouwe Y, Moons KG, Steyerberg EW. External validity of risk models: Use of benchmark values to disentangle a case-mix effect from incorrect coefficients. Am J Epidemiol 2010;172:971–80.
[18] Hosmer DW, Lemeshow S. Applied Logistic regression. New York: John Wiley & Sons Inc; 1989.
[19] Steyerberg EW, Harrell Jr FE, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001;54:774–81.
[20] Jackson A, Skwarchuk M, Zelefsky M, et al. Late rectal bleeding after conformal radiotherapy of prostate cancer (II): volume effects and dose–volume histograms. Int J Radiat Oncol Biol Phys 2001;49:685–98.

[21] Fiorino C, Cozzarini C, Vavassori V, et al. Relationships between DVHs and late rectal bleeding after radiotherapy for prostate cancer: analysis of a large group of patients pooled from three institutions. Radiother Oncol 2002;64:1–12.
[22] Fransson P, Widmark A. 15-year prospective follow-up of patient-reported outcomes of late bowel toxicity after external beam radiotherapy for localized prostate cancer. A comparison with age-matched controls. Acta Oncol 2007;46:517–24.
[23] Buettner F, Gulliford SL, Webb S, Sydes MR, Dearnaley DP, Partridge M. The dose–response of the anal sphincter region – an analysis of data from the MRC RT01 trial. Radiother Oncol 2012;103:347–52.
[24] Dobben AC, Terra MP, Slors JF, Deutekom M, Gerhards MF, Beets-Tan RG, et al. External anal sphincter defects in patients with fecal incontinence: comparison of endoanal R imaging and endoanal US. Radiology 2007;242:463–71.
[25] Yeoh EK, Holloway RH, Fraser RJ, et al. Anorectal function after three- versus two-dimensional radiation therapy for carcinoma of the prostate. Int J Radiat Oncol Biol Phys 009;73:46–52.
[26] Rostaminia G, White D, Quiroz LH, et al. 3D pelvic floor ultrasound findings and severity of anal incontinence. Int Urogynecol J 2013;25:623–9.
[27] Fernández-Fraga X1, Azpiroz F, Malagelada JR, et al. Significance of pelvic floor muscles in anal incontinence. Gastroenterology 2002;123:1441–50.
[28] Fiorino C1, Fellin G, Rancati T, et al. Clinical and dosimetric predictors of late rectal syndrome after 3D-CRT for localized prostate cancer: preliminary results of a multicenter rospective study. Int J Radiat Oncol Biol Phys 2008;70:1130–7.
[29] Ebert MA, Foo K, Haworth A. Gastrointestinal dose-histogram effects in the context of dose-volume-constrained prostate radiation therapy: analysis of data from the RADAR prostate radiation therapy trial. Int J Radiat Oncol Biol Phys 2015;91:595–603.
[30] Baker TA, O'Connor ML, Krok JL. Experience and knowledge of pain management in patients receiving outpatient cancer treatment: what do older adults really know about their cancer pain? Pain Med 2014;15:52–60.
[31] Schaaf van der A, Xu C, Luijk van P, Veld van 't A, Langendijk JA. Multivariate modeling of complications with data driven variable selection: guarding against overfitting and effects of data set size. Radiother Oncol 2012;105:115–21.
[32] Schaaf van der A, Schaake W, van den Bergh A, Langendijk J. Using simulation to guard against spurious data-driven model selection: a case study for rectal toxicity data with high-collinearity and few events. Int J Radiat Oncol Biol Phys 2015;93:S182.

Chapter 5: Development of a prediction model for late urinary incontinence, hematuria, pain and voiding frequency among irradiated prostate cancer patients.

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Abstract

Background and purpose:

Incontinence, hematuria, voiding frequency and pain during voiding are possible side effects of radiotherapy among patients treated for prostate cancer. The objective of this study was to develop multivariable NTCP models for these side effects.

Material and Methods:

This prospective cohort study was composed of 243 patients with localized or locally advanced prostate cancer (stage T1-3). Genito-urinary (GU) toxicity was assessed using a standardized follow-up program. The GU toxicity endpoints were scored using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE 3.0) scoring system. The full bladder and different anatomical subregions within the bladder were delineated. A least absolute shrinkage and selection operator (LASSO) logistic regression analysis was used to analyze dose volume effects on the four individual endpoints.

Results:

In the univariable analysis, urinary incontinence was significantly associated with dose distributions in the trigone (V55-V75, mean). Hematuria was significantly associated with the bladder wall dose (V40-V75, mean), bladder dose (V70-V75), cardiovascular disease and anticoagulants use. Pain during urinating was associated with the dose to the trigone (V50-V75, mean) and with trans transurethral resection of the prostate (TURP). In the final multivariable model urinary incontinence was associated with the mean dose of the trigone. Hematuria was associated with bladder wall dose (V75) and cardiovascular disease, while pain during urinating was associated with trigone dose (V75) and TURP. No significant associations were found for increase in voiding frequency.

Conclusions:

Radiation-induced urinary side effects are associated with dose distributions to different organs as risk. Given the dose effect relationships found, decreasing the dose to the trigone and bladder wall may reduce the incidence of incontinence, pain during voiding and hematuria, respectively.

Introduction

The introduction of intensity modulated radiotherapy (IMRT) and dose escalation has resulted in increased biochemical relapse free survival for localized prostate cancer (1). Despite this increase in tumor control, adjacent organs at risk (OAR) are exposed to high doses that may lead to increased rates of radiation-induced side effects that have an impact on quality of life (2).

To achieve a reduction in side effect rates by adjusting radiotherapy planning, knowledge of the association between complication risk and dose distribution parameters is required.

Traditionally, a distinction is made between gastrointestinal (GI) and genitourinary (GU) side effects. Dose to specific substructures within and around the anorectum are associated with specific gastrointestinal side effects (3). Previous studies on genitourinary side effects showed the dose to the bladder was associated with urinary toxicity among patients treated with external beam radiotherapy (4) (5). Interestingly, dose to the trigone was associated with genitourinary side effects among patients treated with brachytherapy (6,7).

In the vast majority of studies on GU side effects after radiotherapy, toxicity is typically scored as a single cumulative endpoint for all GU side effects taken together, rather than a single score for incontinence, hematuria, pain and increased voiding frequency individually. Presently no multivariable models exists on dose to regions within the bladder and specific late side effects among IMRT treated prostate cancer patients. Therefore, the main objective of this study was to develop multivariable NTCP (Normal Tissue Complication Probability) models for urinary incontinence, hematuria, pain and increased voiding frequency taking into account dose distributions to the bladder as a whole, several regions within the bladder and other candidate prognostic factors.

Materials and methods

Patients

This prospective cohort study was previously described in (3) and was composed of 243 patients with prostate cancer confined to the prostatic capsule (stage T1-3). All patients were treated with radiotherapy between 2005 and 2009. The minimal follow up of patients alive was 3 years. Radiotherapy was delivered using linear accelerators with 6 MV photons by intensity modulated radiotherapy (IMRT). Patients were treated 5 times a week to a total dose of 78 Gy on the planning target volume (PTV), using 2 Gy per fraction. In the current patient cohort, no pelvic lymph nodes were irradiated as part of the treatment. Setup accuracy was verified during delivery by matching bony anatomy or implanted fiducial markers. Most patients with locally advanced prostate cancer received adjuvant hormonal treatment (Table 1). Diabetes was defined as “use of hypoglycemic drugs”, smoking was defined as “any kind of smoking history”. These patient characteristics were retrospectively assessed from detailed patient charts. For the purpose of the current analysis, only patients biochemically failure free at three years after treatment were eligible for this study.

Ethics statement

All patients were subjected to a prospective data registration program in which complications and treatment results in terms of local control and survival are prospectively assessed. This is done within the framework of routine clinical practice in which outcome and complications are systemically scored as part of a quality assurance program. All data obtained and used for this study has been anonymized.

The (Dutch) Medical Research Involving Human Subjects Act is not applicable to data collection as part of routine clinical practice and use of these data for scientific papers regarding the quality assurance program. Only research that is within the scope of the Medical Research Involving Human Subjects Act needs approval from an (accredited) ethics committee. Therefore, the hospital ethics committee (the Medisch Ethische Toetsingscommissie; METc) concluded that data collection by this program is regarded as part of routine patient care and granted us a waiver from needing ethical approval for the conduct of this study.

In the Netherlands a patient of course has to give his/her consent for the collection of the extra data on behalf of the quality assurance program and the use of these data for scientific papers regarding the quality assurance program. However, according to Dutch legislation, consent is free of form, and verbal consent is sufficient. Therefore, patients were asked to participate in this quality assurance program and asked for permission to use their data for the program and scientific papers regarding the program. Refusal of participation was recorded in their medical record.

Table 1: Patient and treatment characteristics

		Number of patients	**%**
Age			
	≤ 70 years	139	57
	>70 years	104	43
Tumor classification			
	T1	92	38
	T2	107	44
	T3	44	18
PSA			
	<4	8	4
	4-10	75	30
	>10	160	66
Gleason			
	5-6	87	36
	7	97	40
	8-10	59	24
Treatment related factors			
	Adjuvant hormonal therapy	104	43
	Fiducial markers	73	30
Pre-treatment related factors			
	History of diabetes	29	12
	Smoking	77	32
	History of cardiovascular disease	82	34
	History of abdominal surgery	90	37
	Anticoagulants use	63	26

TURP	52	21

PSA: Prostate-specific antigen
TURP:transurethral resection of the prostate

Target and organ at risk delineation

Three Planning Target Volumes (PTV) were defined: the PTV46 included the prostate and vesicles, the PTV70 included the prostate and the basis of the vesicles and the PTV78 included the prostate only.

The full bladder was delineated as part of the treatment planning. Patients were instructed to urinate and drink half a liter of water one hour prior to radiotherapy. The bladder wall was created using an inner ring within the full bladder of 3.3mm (8). The trigone was defined as the triangle-shaped structure between the transition of the ureters in the bladder wall cranially and the transition of the urethra into the bladder wall caudally (9) (Figure 1).

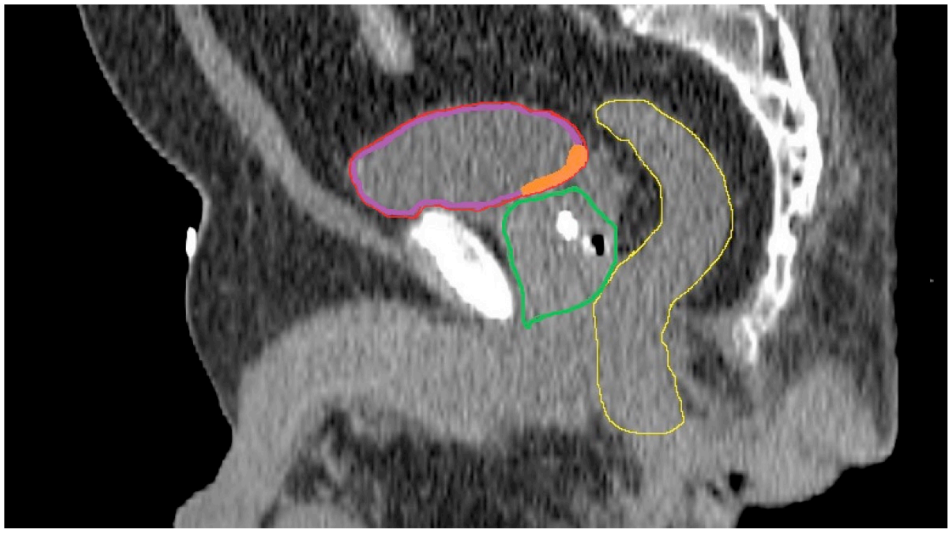


Figure 1 Sagittal view of the bladder (red), bladderwall (purple), trigonum (orange), prostate (green), anorectum (yellow).

Endpoints

Side effects were assessed prospectively using questionnaires filled out by patients treated between 2005 and 2009. The questionnaires have been previously used in a multicenter randomized phase III trial (10) and at our institute (11). Using these questionnaires, the different endpoints were scored according to the

Common Terminology Criteria for Adverse Events version 3.0 (CTCAE 3.0) scoring system (12). Late toxicity was assessed at six months, 12 months, 24 months and 36 months after treatment, finally resulting in a single maximum toxicity score per endpoint over the entire three years. The minimal follow up of patients alive was 3 years.

Urinary incontinence grade ≥ 2 was defined as spontaneous loss of urine and when use of pads was indicated. Hematuria grade 1 was defined as minimal bleeding when no intervention was indicated, while hematuria grade 2 was defined as bleeding requiring medical intervention. Pain or discomfort during urinating grade 1 was defined as mild pain not interfering with function, while pain grade ≥2 was defined as pain interfering with instrumental activities of daily living (ADL). Finally, voiding frequency increase was defined as an increase of >2 times normal (grade ≥2).

Statistical analysis

The candidate prognostic factors of the four endpoints in our analysis were selected based on available literature on GU-NTCP modeling (4-6) and included the mean dose for each organ at risk and the relative volumes receiving 5-70 Gy, in 5 Gy bins (V5-V70). Additionally, we included age, adjuvant hormonal treatment, and pre-treatment factors (Table 1) as candidate predictors, which were retrieved retrospectively from the patient charts.

To show the crude effect of each endpoint, a univariable logistic regression analysis was performed on every endpoint. For the development of the multivariable prediction models the least absolute shrinkage and selection operator (LASSO) method in R was used, available in the Lasso and Elastic-Net Regularized Generalized Linear Model package, version 2.0-2 (13). This is a logistic regression analysis with a penalty for the magnitude of the regression coefficients to prevent overfitting (14). Because of the high collinearity of the candidate predictors, the set of variables was reduced prior to the LASSO analysis; from the dose variables that had an intercorrelation > 0.80 only the most significant predictor (as measured by the p-value in univariable analysis) remained a candidate prognostic factor.

Subsequently, the variables selected by LASSO were fitted again to the data with logistic regression and internally validated through bootstrapping. This validation gives a measure of optimism of the model, which can be used to correct the coefficients of the model performance accordingly. Model performance was described using various validation measures (15) (16). The discriminating ability of the model was

described by the Area Under the receiver operating characteristic Curve (AUC). Nagelkerke's R^2 was calculated as a pseudo measure of explained variance. The gain and intercept of the model calibration were calculated, and the calibration was evaluated using a Hosmer-Lemeshow test (17). Results with $p<0.05$ were considered as significant.

Finally, for each endpoint a NTCP curve was constructed based on the corrected regression coefficients from then internal validation (formula 1).

$$\text{NTCP} = \frac{1}{(1+e^{-S})} \qquad \text{(formula 1)}$$

Results

Urinary incontinence

Twenty nine out of 243 patients (12.0 %) experienced grade 2 or higher urinary incontinence. The candidate predictors of urinary incontinence included dosimetric predictors of all bladder structures and pre-treatment variables diabetes, age, cardiovascular disease, abdominal surgery, adjuvant hormonal treatment and TURP. Nine patients experienced grade ≥ 2 incontinence prior to radiotherapy. As these patients already experienced the endpoint of the model before treatment, they were excluded from the multivariable model on incontinence. In the univariable analysis and the V55-V75 and mean dose of the trigone were associated with urinary incontinence (Table 2).

The final multivariable analysis resulted in a model with one predictor (Figure 2), i.e. the trigone mean dose (Confidence Interval (CI) Odds Ratio (OR): 1.02-1.20), with a corrected AUC of 0.66 (CI: 0.58-0.78) and a corrected R-square of 0.10 (Table 3).

In individual cases, the risk of urinary incontinence can be estimated using formula 1, where S is defined as:

$$S = -9.67 + 0.1015 \cdot (\text{trigone (mean)})$$

The Hosmer-Lemeshow test was not significant (chi square of 4.91.71; degrees of freedom (df) = 8; p=0.77), indicating good agreement between expected and observed complication rates.

Table 2: Univariable logistic regression analysis for urinary incontinence, hematuria and pain during voiding. Only p-values < 0.05 are shown.

		Odds ratio (OR)*	CI	p-Value
Urinary Incontinence ≥ grade 2 (n=20)				
Trigone	Mean dose	1.11	1.02-1.20	0.015
	V55	1.08	1.01-1.16	0.027
	V60	1.06	1.01-1.11	0.016
	V65	1.05	1.01-1.08	0.010
	V70	1.03	1.01-1.05	0.008
	V75	1.01	1.00-1.02	0.042
Hematuria ≥1 (n=23)				
Cardiovascular disease		2.845	1.19-6.80	0.019
Anticoagulants use		2.424	1.01-5.85	0.049
Bladderwall	Mean dose	1.028	1.00-1.06	0.032
	V40	1.017	1.00-1.03	0.040
	V45	1.019	1.00-1.04	0.024
	V50	1.020	1.00-1.04	0.015
	V55	1.021	1.00-1.04	0.014
	V60	1.022	1.01-1.04	0.011
	V65	1.024	1.01-1.04	0.007
	V70	1.026	1.01-1.04	0.004
	V75	1.027	1.01-1.04	0.002
Bladder	V70	1.015	1.00-1.03	0.029
	V75	1.015	1.00-1.03	0.021
Pain during voiding				
TURP		2.46	1.01-5.99	0.048
Trigone	Mean dose	1.106	1.03-1.19	0.008
	V50	1.048	1.00-1.10	0.043
	V55	1.047	1.01-1.09	0.024
	V60	1.042	1.01-1.08	0.015
	V65	1.038	1.01-1.07	0.008
	V70	1.030	1.01-1.05	0.003
	V75	1.021	1.01-1.03	0.001

For dose variables OR: increase per 1 Gy increase in dose, for volume parameters: increase per 1% increase in volume
TURP: transurethral resection of the prostate

Table 3: Performance and calibration measures for the multivariable model for urinary incontinence, hematuria and pain during voiding. Apparent measures were calculated using the complete dataset on which the model was trained; the corrected measures were adjusted for optimism as calculated with a bootstrapping procedure.

Performance and calibration measure	Urinary incontinence		Hematuria		Pain during voiding	
	Apparent	Corrected	Apparent	Corrected	Apparent	Corrected
AUC*	0.66	0.66	0.72	0.71	0.77	0.76
Nagelkerkes R^2	0.11	0.10	0.13	0.10	0.16	0.13
Discrimination Slope	0.04	0.04	0.08	0.08	0.08	0.08

AUC: Area under the Curve

Hematuria

In total, 23 out of 243 (9.5%) patients experienced grade ≥ 1 hematuria, of which 3 (1%) grade 2. Because of the low number of patients with grade 2 toxicity (3), we decided to use grade ≥ 1 hematuria as primary endpoint for this analysis. The candidate predictors for hematuria included dosimetric predictors of all bladder (sub)structures and other pre-treatment variables, including diabetes, age, cardiovascular disease, abdominal surgery, adjuvant hormonal treatment, anticoagulants and TURP.

In the univariable analysis grade ≥ 1 hematuria was associated with the V40-V75 and mean dose of the bladder wall and the V70-V75 of the bladder (Table 2). In addition, significant associations were found with cardiovascular disease and anticoagulant use.

The final multivariable analysis resulted in a model with two predictors (Figure 2), including the bladder wall V75 (CI OR 1.03-1.03) and cardiovascular disease (CI 3.12-3.31), with a corrected AUC of 0.71 (CI: 0.62-0.84) and a corrected R-square of 0.10 (Table 3). In individual cases, the risk of hematuria can be estimated using formula 1, where S is defined as:

$$S = -3.45 + 0.028 \cdot \left(\text{bladderwall(V75)}\right) + 1.15 \cdot (\text{cardiovascular disease}))$$

With bladder wall(V75) in relative volume % and cardiovascular disease is 1 (yes) or 0 (no).

The Hosmer-Lemeshow test had a chi square of 4.96 (df=8, p=0.76), indicating good agreement between expected and observed complication rates.

Pain or discomfort during voiding.

A total number of 24 out of 243 patients (9.9%) experienced moderate discomfort or pain during voiding (≥ grade 2). The candidate predictors of pain or discomfort during voiding included dosimetric predictors of all bladder (sub)structures and a number of other pre-treatment variables including diabetes, age, cardiovascular disease, abdominal surgery, adjuvant hormonal treatment and TURP.

In the univariable analysis the V50-V75, mean dose of the trigone and TURP were significantly associated with increased pain or discomfort during voiding (Table 2).

The final multivariable analysis resulted in a model with two predictors (Figure 2), including TURP (CI OR 1.18-7.83) and trigone (V75) (CI OR 1.01-1.04), with a corrected AUC of 0.76 (CI: 0.67 – 0.86) and a corrected R-square of 0.13 (Table 3). In individual cases, the risk of pain or discomfort during voiding can be estimated using formula 1, where S is defined as:

$$S = -3.87 + 0.021 \cdot (\text{trigone(V75)} + 1.06 \cdot (\text{TURP})$$

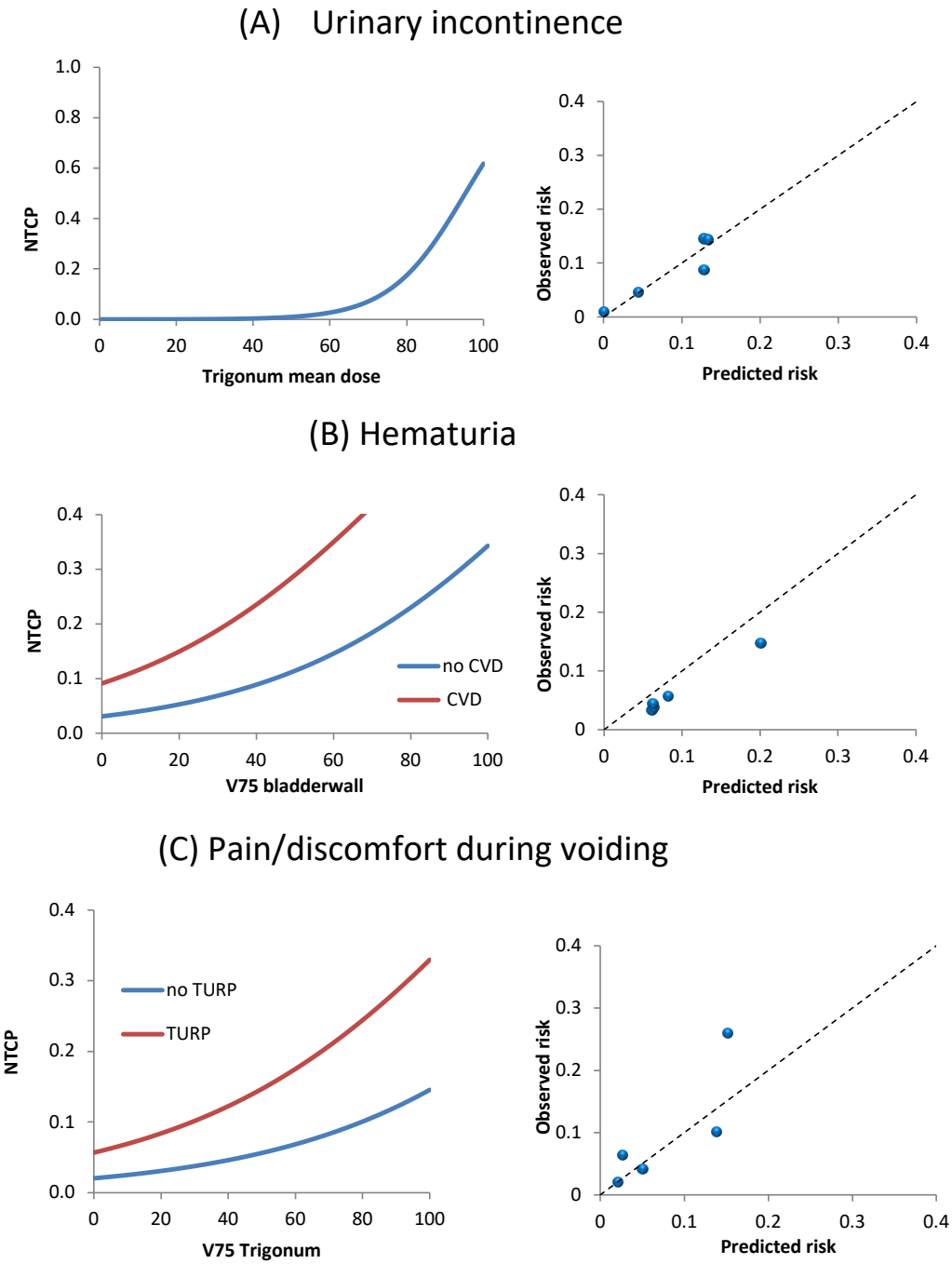
With trigone(V75) in relative volume % and TURP is 1 (yes) or 0 (no).

The Hosmer-Lemeshow test was not significant (chi square 7.84; df 8; p=0.48), indicating good agreement between expected and observed complication rates.

Increase in voiding frequency (night and day)

In the univariable and multivariable analysis no significant associations were found for any of the dosimetric or pre-treatment predictors with voiding frequency.

Figure 2: Final logistic regression analysis for urinary incontinence, hematuria and pain/discomfort during voiding. The left graphs represent relative volumes with corresponding NTCP risk. The right graphs respresent calibration plots for internal validation. The blue points represent the Hosmer–Lemeshow groups and the dashed line represents the identity line.
CVD: cardiovascular disease. TURP: Transurethral resection of the prostate



Discussion

The main objective of this study was to develop multivariable NTCP models for urinary incontinence, hematuria, pain or discomfort during voiding and increase in voiding frequency based on different subregions within the bladder. Urinary incontinence was best predicted by the trigone mean dose. Hematuria was best predicted by the bladder wall V75 and cardiovascular disease. Pain or discomfort during voiding was best predicted by the trigone V75 and cardiovascular disease. No associations were found for increase in voiding frequency.

Our data show that the dose to the trigone may have an impact on the occurrence of GU complaints, which is in line with research on patients with high-dose IMRT (86.4 Gy) (9) and with brachytherapy (6,7). In both studies complaints were scored using the IPSS (International Prostate Symptom Score (IPSS)), resulting in a single (side effect) score for each patient. As different GU side effects have a different pathophysiology (18), relating each side effect individually to different dose parameters may be more appropriate and results in more appropriate associations between dose-volume parameters and specific side effects.

Urinary incontinence may originate in the trigone of the bladder, as the lower part contains the involuntary internal or pre-prostatic sphincter (18). A decrease in dose to this region may likely decrease the incidence of urinary incontinence. However, the external sphincter of the bladder may also play a role in urinary incontinence as it controls the voluntary control of voiding. The external sphincter lies directly beneath the prostate and thereby receives high doses. As this structure is hard to distinguish on CT images we were not able to investigate the impact of dose to this region. The use of MRI in delineating target organs may offer better opportunities to analyze the effect of external sphincter dose-volume parameters on incontinence, as the external sphincter can be better identified with MRI (18).

External beam radiotherapy can cause hematuria (19-20), which is most likely related to the high dose areas within the bladder (21). In the latter study the volume of the whole bladder receiving ≥ 75 Gy was the best predictor for hematuria. Although the univariable analysis of the present study showed similar results, no such relationship was found in the final multivariable model, which actually showed that the dose to the bladder wall was a better predictor of hematuria than the entire bladder dose. These results suggest that the dose to the entire bladder is a surrogate for the importance of the dose to the bladder wall. From a pathophysiological point of view, it seems evident that dose hotspots to the bladder wall are more indicative of side effects (22-23). Anticoagulants use was significantly related to hematuria in the univariable analysis, which is in accordance with a study by Palorini (24). In that study, cardiovascular drugs

were found as risk factors for a decreased IPSS score, indicating a possible impaired healing process of radiation-induced damage in patients with microangiopathic disease. Interestingly, anticoagulants were not significant anymore in our multivariable model. This may be caused by the fact that a significant number of patients with cardiovascular disease used anticoagulants. Cardiovascular disease NTCP models performed better than NTCP models with anticoagulants, indicating the importance of taking into account cardiovascular disease in treatment of prostate cancer patients (25-26).

The question may arise what the impact is of volume and motion of the bladder on finding dose-volume relations. A study by Palorini (27) on bladder motility during treatment showed that the cranial and anterior part of the bladder exhibits large systematic variation. The caudal part of the bladder however is relatively independent of bladder filling and may therefore be a reliable predictor in optimizing prostate radiotherapy. The trigone is a relatively rigid part of the bladder, as the bladder neck is surrounded by the prostate and encompassing puboprostatic ligaments (28). A study on prostatectomy shows that sparing of these ligaments may result in less urinary incontinence (29). Taking these results into account, the dose to the trigone that we found to be predictive of urinary incontinence and pain, may be a surrogate for these ligaments. However, these ligaments were not visible on CT and were therefore not investigated as an organ at risk for any of the four endpoints.

Although increase in voiding frequency is reported frequently as a side effect resulting from prostate radiotherapy, we were not able to find an association between dose to different anatomical regions and increase in voiding frequency. In a recent study using a pixel-wise analysis of dose-surface maps (30), a relation was found between the dose to the posterior bladder at 5-12 mm from the base and an acute increase in voiding frequency. Therefore, future research should focus on this endpoint to confirm this dose-volume relation in order to prevent a decrease in quality of life of prostate cancer patients.

A limitation of this study was the low number of events for each endpoint. The internal validation showed that for these data the models performed relatively well and despite the low number of events the robustness in this dataset was relatively large (3)(31). There are different ways to analyze dose-effect relationships, e.g. LASSO, bootstrapping and “simple” backward regression analysis. To check the robustness of our analysis, all of the aforementioned procedures were tested in our data and all led to more or less the same results, indicating our results were relatively independent of the type of analysis that was used and relatively independent of the low number of events. However, external validation in other datasets is warranted. We are currently working on a study to validate our data externally as was done at our institute for head and neck cancer patients (32).

Another limitation of this study is the variability of the bladder volume during treatment. Research has shown that patient motion, bladder centroid motion and bladder filling may have an impact on pretreatment imaging (33). We recommend researchers to take this into account in future studies on prostate NTCP-modeling by using daily imaging techniques and deformable image registration.

This study shows that different anatomical subregions within the bladder are related to different side effects. Urinary incontinence and pain during voiding is related to dose to the trigone and hematuria is related to the dose in the bladder wall. This information can be used in treatment plan optimization. Additional prospective studies are needed to confirm that dose reductions to these regions result in less side effects.

References

[1] Zelefsky MJ, Pei X, Chou JF, et al. Dose Escalation for Prostate Cancer Radiotherapy: Predictors of Long-Term Biochemical Tumor Control and Distant Metastases–Free Survival Outcomes. European Jorunal of Urology 2011, 60(6);1133-1139.

[2] Schaake W, Wiegman EM, Groot de M,et al. The impact of gastrointestinal and genitourinary toxicity on health related quality of life among irradiated prostate cancer patients. Radiotherapy and Oncology 2014, 110; 284-290.

[3] Schaake W, van der Schaaf A., L. V. van Dijk et al. Normal tissue complication probability (NTCP) models for late rectal bleeding, stool frequency and fecal incontinence after radiotherapy in prostate cancer patients. Radiotherapy and Oncology 2016, 119(3):381-7.

[4] Heemsbergen WD, Al-Mamgani A, Witte MG et al. Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): relationships with local dose, acute effects, and baseline characteristics. Int. J. Radiation Oncology Biol. Phys 2010, 78(1):19-25.

[5] Fiorino C, Valdagni R, Rancati T. et al. Dose–volume effects for normal tissues in external radiotherapy: Pelvis. Radiotherapy and Oncology 2009, 93; 153-167.

[6] Hathout L, Folkert MR, Kollmeier MA et al. Dose to the bladder neck is the most important predictor for acute and late toxicity after low-dose-rate prostate brachytherapy: implications for establishing new dose constraints for preatment planning. Int. J. Radiation Oncology Biol. Phys. 2014, 90(2), 312-319.

[7] MJ Steggerda, T Witteveen, F van den Boom et al. Is there a relation between the radiation dose to the different sub-segments of the lower urinary tract and urinary morbidity after brachytherapy of the prostate with I-125 seeds? Radiotherapy and Oncology 2013, 109(2): 251–255.

[8] Hakenberg OW, Linne C, Manseck A et al. Bladder wall thickness in normal adults and men with mild lower urinary tract symptoms and benign prostatic enlargement. Neurourology and Urodynamics 2000, 19;585–593.

[9] Ghadjar P, Zelefsky MJ, Spratt DE et al. The impact of dose to the bladder trigone on long-term urinary function after high-dose intensity-modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2015, 88(2): 339–344.

[10] Peeters STH, Heemsbergen WD, Putten van WLJ et al. Acute and late complications after radiotherapy for prostate cancer: Results of a multicenter randomized trial comparing 68 Gy to 78 Gy. International Journal of Radiation Oncology, Biology and Physics 2005, 61(4); 1019-1034.

[11] Grading-system-dependent volume effects for late radiation-induced rectal toxicity after curative radiotherapy for prostate cancer. Laan van der HP, Bergh van den ACM, Schilstra C et al. International Journal of Radiation Oncology,Biology and Physics 2008, 70(4); 1138-1145.

[12] CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Trotti A, Colevas AD, Setser A et al. Seminars in Radiation Oncology 2003, pp. 13(3); 176-181.

[13]http://www.R-project.org/.

[14] Tibshirani, R. Regression shrinkage and selection via the lasso. J. R. Statist. Soc. B 1996, 58; 267–288.

[15] Steyerberg EW, Vickers AJ, Cook NR et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. Epidemiology 2010, 21(1); 128-138.

[16] Vergouwe Y, Moons KG, Steyerberg EW. External validity of risk models: Use of benchmark values to disentangle a case-mix effect from incorrect coefficients. American Journal of Epidemiology 2010, 172(8); 971-980.

[17] Hosmer, DW, Lemeshow S. Applied Logistic regression. s.l. 1989: New York : John Wiley & Sons, Inc.

[18] Mclaughlin PW, Troyer S, Berri S et al. Functional anatomy of the prostate: implications for treatment planning. Int. J. Radiation Oncology Biol. Phys 2005, 63(2): 479–491.

[19] Leapman MS, Hall SJ, Stone NN et al. Haematuria after prostate brachytherapy. 2013, BJU International 2013, 111: 319-324.

[20] Mathieu R, Arango JDO, Beckendorf V et al. Nomograms to predict late urinary toxicity after prostate cancer radiotherapy. World Journal of Urology 2014, (32)3; 743-751.

[21] De Langhe S, De Meerleer G, De Ruyck K et al. Integrated models for the prediction of late genitourinary complaints after high-dose intensity modulated radiotherapy for prostate cancer: Making informed decisions. Radiotherapy and Oncology 2014, 112(1): 95–99.

[22] Predictors for chronic urinary toxicity after the treatment of prostate cancer with addaptive three-dimensional conformal radiotherapy: dose-volume analysis of a phase II dose-escalation study. Harsiola A, Vargas C, Yan D et al., Int. J. Radiation Oncology Biol. Phys 2007, 69(4): 1100–1109.
[23] Ahmed AA, Egleston B, Alcantara P et al. A novel method for predicting late genitourinary toxicity after prostate radiation therapy and the need for age-based risk-adapted dose constraints. Int J Radiat Oncol Biol Phys 2013, 86(4):709-715.
[24] Palorini F, Rancati T, Cozzarini C et al. Multi-variable models of large International Prostate Symptom Score worsening at the end of therapy in prostate cancer radiotherapy. Radiotherapy and Oncology 2016, 118; 92-98.
[25] Schaake W, de Groot M, Krijnen WP. Quality of life among prostate cancer patients: a prospective longitudinal population-based study., Radiotherapy and Oncology 2013, 108(2):299-305.
[26] Gurka MK, Chen LN, Bhagat A. et al. Hematuria following stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer. Radiation Oncology 2015, (10):44.
[27] Palorini F, Botti A, Carillo V et al. Bladder dose-surface maps and urinary toxicity: Robustness with respect to motion in assessing local dose effects. Physica Medica 2016, 32(3): 506-11.
[28] The puboprostatic ligament and the male urethral suspensory mechanism: an anatomic study. MS Steiner. Urology 1994, 44(4):530-4.
[29] Poore RE, McCullough DL, Jarow JP. Puboprostatic ligament sparing improves urinary contience after radical retropubic prostatectomy. Urology 1998, 51(1):67-72.
[30] Palorini F, Cozzarini C, Gianolini C et al. First application of a pixel-wise analysis on bladder dose-surface maps in prostate cancer radiotherapy. Radiotherapy and Oncology 2016, 119(1):123-8.
[31] Schaaf van der A, Schaake W, van den Bergh ACM et al. Using simulation to guard against spurious data-driven model selection: A case study for rectal toxicity data with high-collinearity and few events. Int J Radiat Oncol Biol Phys 2015;93(3):S182.
[32] Wopken K, Bijl HP, van der Schaaf A et al. Development and validation of a prediction model for tube feeding dependence after curative (chemo-) radiation in head and neck cancer. Plos One 2014; 9(4).
[33] Foroudi F, Pham D, Bressel M. et al. Intrafraction bladder motion in radiation therapy estimated from pretreatment and posttreatment volumetric imaging. Int. J. Radiation Oncology Biol. Phys 2013, pp 86(1):77-82.

Chapter 6: Summarizing discussion and future perspectives

Introduction

This thesis was performed to investigate the course of quality of life among prostate cancer patients treated with radiotherapy, to investigate which side effects have the largest impact on quality of life and ultimately to develop multivariable NTCP-models for prostate cancer patients treated with definitive radiotherapy.

Summary of main findings

In **chapter 2** the difference in quality of life between prostate cancer survivors and a normative cohort of men was analysed. In this longitudinal case-control study, we showed that the quality of life of patients after radiotherapy is declined as compared to their quality of life before treatment and as compared to the normative cohort. Additional analyses showed that co-morbidity such as coronary heart disease and COPD have an influence on the course of this decline.

In **chapter 3** we investigated possible causes for the decline in quality of life after radiotherapy. In this study, using a multivariate approach, the relationship between different side effects and quality of life was presented. Both gastrointestinal and genitourinary toxicity had a significant impact on the quality of life of patients after completion of the treatment.

Chapter 4 shows the relationship between different dose volume parameters within and around the anorectum and gastrointestinal side effects. Different anorectal side effects were associated with different anatomical substructures; rectal bleeding was associated with high doses to the anorectum and anticoagulants use, anal incontinence was associated with the dose levels to the external anal sphincter and iliococcygeal muscle. Finally, stool frequency was associated with intermediate doses to the levator ani muscles.

In **chapter 5** dose volume parameters of the bladder were related to genitourinary side effects. Different urinary side effects were associated with different anatomical substructures within the bladder; urinary incontinence was associated with the mean dose to the trigone, while haematuria was associated with high doses to the bladder wall and with cardiovascular disease. Finally pain during voiding was associated with high doses to the trigone and a history of TURP.

Discussion

The life expectancy of patients with localized or locally advanced prostate cancer is relatively favourable in comparison with that of patients with other cancer types. In recent decades, the introduction of radiation dose escalation in prostate cancer has resulted in a 10-year PSA relapse-free survival of 84% [1]. Considering this relatively good prognosis, other endpoints of (radio)therapy have become more important in the selection process of the different treatment options. In radiotherapy, genitourinary and gastrointestinal side effects are commonly reported by prostate cancer patients [2, 3]. However, limited data existed on the impact of these side effects on patients' quality of life. Prevention of these side effects is particularly important when patients' quality of life is negatively affected. Therefore, it is essential to gain more information about the extent to which dose-volume parameters are associated with radiation-induced toxicities [4, 5]. The relationship between radiation dose to specific anatomical structures and the probability of developing certain side effects can be described by so-called Normal Tissue Complication Probability (NTCP) models. Accurate prediction of the risks of radiation-induced side effects may offer opportunities to optimize dose distributions to minimize radiation-induced side effects, to select the best technique and to identify patients that will benefit most from new radiation delivery techniques, such as protons, which were introduced in the Netherlands in 2018.

Quality of life of prostate cancer patients before and after radiotherapy

The interpretation of the impact of an improvement or deterioration in quality of life during a patients' life is often difficult without a clear normative benchmark. Therefore, in this thesis, we compared the quality of life of a normative group of men with that of prostate cancer patients treated with radiotherapy (**Chapter 2**). Our study showed that, considering possible (in)equality at baseline, quality of life of patients is only minimally impaired as compared to the normative group and as compared to baseline regarding the general aspects of daily functioning. This may imply that prostate cancer radiotherapy is relatively well endured by patients. However, several aspects such as social and role functioning may deteriorate and require special attention. To investigate the possible causes for this decline it is essential to know which and to what extent toxicity endpoints affect patients' quality of life. Traditionally, rectal bleeding is regarded as the most important side effect in prostate radiotherapy, which is reflected by the number of studies on this topic [6][7][8][9][10][11][12]. Although severe rectal bleeding is clinically relevant, mild or moderate urinary incontinence and rectal discomfort may influence a patient's quality of life more than

rectal bleeding (**Chapter 3**). Therefore, next to attention to rectal bleeding, more attention is needed on the prevention of urinary incontinence and rectal discomfort as well.

Gastrointestinal side effects

Predicting gastrointestinal side effects by means of NTCP models requires a clear definition of the organs at risk (OAR) and a clear definition of endpoints. The anorectum may be divided in a lower (anal) and upper (rectum) part [9, 10]. Analyses on dose to other substructures such as the anterior rectal wall present interesting dose effect relations [11]. Additionally, Smeenk et al. found significant dose-effect relationships between the pelvic floor muscles with faecal incontinence and high stool frequency [12].

The anorectum is encompassed by a wide variety of muscles and defecation is a complex activity controlled by voluntary and involuntary sphincters around the anus. Taking into account this relatively complex activity, the question arises which of these potential OAR's is most important for the development of radiation-induced gastrointestinal side effects and if radiotherapy treatment planning can be optimized if the dose is minimized in specific substructures within or around the anorectum. Given the aforementioned studies on dose effect relationships and the theoretical basis for late anorectal dysfunction [13], we decided to not only consider the most frequently investigated composed OAR's, but also to investigate the relationship between the doses to different muscles around the anorectum and the risk on gastrointestinal side effects, in particular with regard to anal incontinence **(Chapter 4)**.

All investigated predictors, both "traditional" and "new", performed relatively well in our analysis. The prognostic significance of the traditional predictor, i.e. the dose to the anorectum was confirmed in the univariable analysis on rectal bleeding with higher doses to the anorectum resulting in higher probabilities of developing grade ≥ 2 rectal bleeding. Dosimetrics of more detailed substructures, such as of the rectal wall, the anus or rectum, were less predictive of rectal bleeding, in terms of model performance.

In contrast, faecal incontinence and high stool frequency showed a better performance for the dose to the substructures than the dose to the composed larger OAR's. The multivariable analysis showed that a particular subset of the pelvic floor muscles, i.e., the iliococcygeal muscle, the levator ani muscle and the external sphincter, were significantly associated with these two endpoints. These pelvic floor muscles join at different places and work together to support the pelvic viscera and to maintain faecal continence [14, 15]. The majority of (midrange) pelvic floor dose parameters were associated with these endpoints in the univariable model, in line with the results found by Smeenk, et al. [12]. Given the close anatomical and functional relationship, we cannot rule out the influence of dose to one of the pelvic floor muscles, such as the puborectal muscle and internal sphincter, which were ultimately not included in the final model.

We were not able to find associations between dose to structures within or around the anorectum and rectal pain. Comparable results were found in the RADAR (Randomised Androgen Deprivation and Radiotherapy) [16] trial. Recently, Cicetti [17] found an impact of midrange dose volume factors on stool frequency and rectal pain. The inclusion of a large sample of patients (n=1336) and the use of a different toxicity scoring system (i.e. Late Effects of Normal Tissue/Subjective, Objective, Management and Analytic: LENT/SOMA scale) may explain the different outcomes among these studies [18,19].

The models presented in our final analyses are all highly stable in the internal validation, but they should be interpreted with some caution. The dose to the pelvic floor muscles has a clear impact on faecal incontinence and high stool frequency, but an external validation study is required to confirm the relatively simple models presented in our final analysis.

Given the shape of the dose response curve of the NTCP-model presented, patients with a high V70 to the anorectum may particularly benefit from planned dose optimisation as compared to patients with an already low V70 (figure 1).

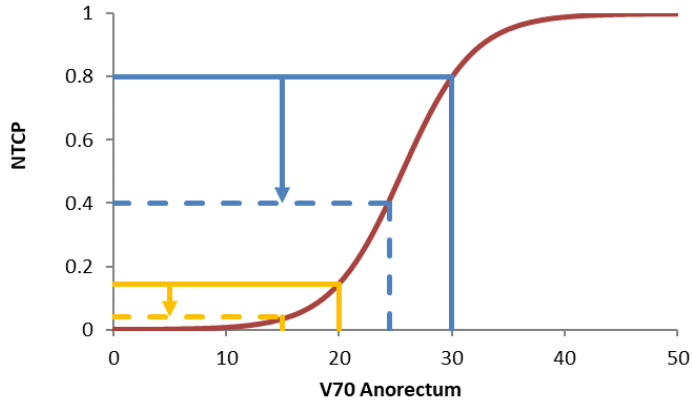


Figure 1: NTCP rectal bleeding reduction with 5% decrease in dose to the V70 of the anorectum. Blue represents a patient with an expected NTCP reduction of 40%. Yellow represents a patient with an expected NTCP reduction of 10%.

Altering radiotherapy treatment planning guided by NTCP models may result in a marked reduction in treatment related side effects. However, complete prevention of side effects is not awaited and therefore other treatment options in relation to side effects require extra attention. Treatment options for patients

with grade ≥ 2 rectal bleeding may involve steroid enemas and one or more argon plasma coagulations (APC) and these are generally regarded as effective and are widely used after diagnosis of radiation induced rectal bleeding [20]. Treatment of faecal incontinence and high stool frequency after radiotherapy is less evident in clinical practice. A review on pelvic floor muscle training and biofeedback therapy showed a positive effect for most patients with any kind of faecal incontinence [21]. In this way, the continuation of faecal incontinence after prostate radiotherapy could be halted or decreased. Rectal pain may be countered by means of medicines such as analgesia and amifostine [22] More recently, synbiotics have also been shown to improve quality of life after prostate cancer radiotherapy [23].

Genitourinary side effects

Genitourinary side effects are less under investigation in comparison with gastrointestinal side effects [8]. An explanation might be that, due to bladder volume variability, an estimation of the actual given dose is difficult [24]. Despite these difficulties, significant relationships were found between the dose to specific structures within the bladder and genitourinary side effects in patients treated with brachytherapy [25]. However, limited data exist on equivalent relationships after external beam radiotherapy. One study, in patients treated with 48 fractions of 1.8 Gy to a total dose of 86.4 Gy, showed [26] a significant relationship between the dose to the lower parts of the bladder and genitourinary side effects. In our study (**Chapter 5**), for patients treated in 39 fractions to a total dose of 78 Gy we found comparable effects; the dose to the trigonum was predictive for incontinence and pain during urinating.

Based on the significant impact of urinary incontinence on the more general dimensions of quality of life as found in our study (**Chapter 3**), this side effect deserves more attention.

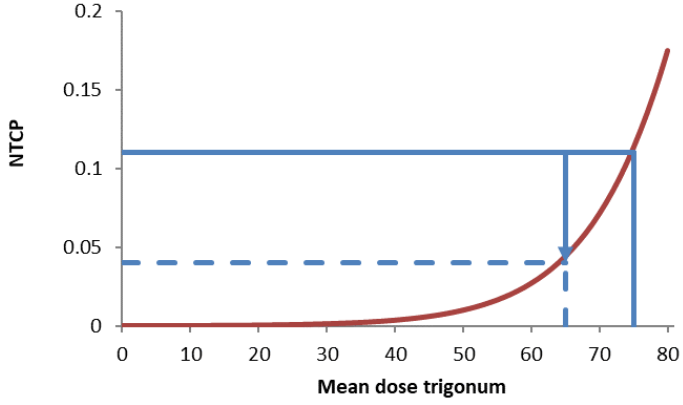


Figure 2: NTCP urinary incontinence reduction with 10 Gy decrease in mean dose to the trigonum (75Gy -> 65Gy). An NTCP reduction of 0.06 is possible for this patient.

Additionally, we found an impact of bladder wall dose on haematuria comparable with studies by Ahmed [27] and Harsiola [28]. Although it is theoretically possible to decrease the dose to different bladder structures (figure 2) the practicability is questionable. The trigonum is in close vicinity to the prostate and consequently it may be difficult to prevent delivery of radiation to this substructure. This problem may be countered by proton therapy, which offers the opportunity to deliver most of its energy at a certain depth. Planning studies by Scobioala [29] and Yeo [30] showed that proton therapy decreased a range of dose variables to the entire bladder compared to photon therapy. Evidence on more specific substructures as analysed in our study are lacking in current prostate cancer literature.

The mobility of the bladder and the variation in bladder filling are another challenge in prostate cancer radiotherapy. Fluid intake prior to radiotherapy is often applied, as it causes a comparable anatomy to planning. A study by Palorini [31] on bladder motility during treatment showed that the cranial and anterior part of the bladder exhibits large systematic variation. The caudal part of the bladder, however, is relatively independent of bladder filling and may therefore be a reliable substructure in optimizing prostate radiotherapy [32].

Although our aim was to identify structures that cause genitourinary toxicity, we did not investigate the impact of dose to penile structures/neurovascular bundle/vascular structures on impotence or orgasmic dysfunction. Impotence and orgasmic dysfunction are part of a patient's sexual functioning and have an impact on their and their partner's quality of life after prostate radiotherapy [33]. Recent studies [34, 35] show that dose to the corpus cavernosum, the penile bulb and the total penile structure are predictive of a decreased sexual functioning after radiotherapy. Proton therapy may decrease the dose to the penile structures and may thereby offer the opportunity to even further enhance a patients' quality of life after radiotherapy.

Conclusions and future perspectives

This thesis is the first important step of the model-based approach in curative prostate cancer treatment [4]; i.e., which patients will benefit most from organ at risk sparing? The NTCP-models on gastrointestinal and genitourinary side effects showed high model performance and suggested that a decrease in dose to specific substructures of the organs at risk may result in a clinically relevant decrease in complication probability. This information is important, given the trend in hypofractionation and the introduction of proton therapy in the Netherlands and around the world. However, external validation in independent

cohorts of prostate cancer patients is warranted [36]. In addition, an estimation of the practicability of the given models in an in silico planning comparative study (ISPC) should be performed before introducing these models in practice or into new radiation delivery techniques. Part of the (sub) structures under investigation in our study were analysed in the same way by Scobioala and Yeo; Protons offer the opportunity to reduce dose to the anorectum and bladder wall with preservation of a homogeneous and highly conformal dose distribution [29] [30]. A study by Schwarz [37] showed that 5 field IMPT (Intensity modulated proton therapy) resulted in a reduction of more than 50% to the V70 of the rectum. The last step in determining model-based indications for new delivery techniques is the estimation of the clinical benefit of these models. This has not been investigated in the current literature and should be investigated in future research.

References

[1] Zelefsky MJ, Pei X, Chou JF, Schechter M, Kollmeier M, Cox B, et al. Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. Eur J Urol 2011;60:1133–9.

[2] Spratt DE, Pei X, Yamada J, et al. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2013; 85:686–92.

[3] Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008; 70:1124–9.

[4] Widder J, van der Schaaf A, Lambin P, Marijnen CAM, Pignol J, Rasch CR, Slotman BJ, Verheij M, Langendijk JA. The quest for evidence for proton therapy: Model-based approach and precision medicine. Int J Radiat Oncol Biol Phys 2016; 1: 30-36.

[5] Langendijk JA, Lambin P, De Ruysscher D et al.. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol 2013; 107: 267-273.

[6] Cheung R, Tucker S, Ye J et al: Characterization of rectal normal tissue complication probability after high-dose external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2004; 58(5):1513-19.

[7] Peeters S, Hoogeman M, Heemsbergen W et al: Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: Normal tissue complication probability modeling. Int J Radiat Oncol Biol Phys 2006; 66(1):11-19.

[8] Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose–volume effects for normal tissues in external radiotherapy: pelvis. Radiotherapy and Oncology 2009; 93:153–67.

[9] Stenmark MH, Conlon ASC, Johnson S, Daignault S, Litzenberg D, Marsh R, Ritter T, Vance S, Kazzi N, Feng F, Sandler H, Sanda MG, Hamstra DA. Dose to the inferior rectum is strongly associated with patient reported bowel quality of life after radiation therapy for prostate cancer. Radiotherapy and Oncology 2014. 110; 291-297.

[10] Wortel RC, Witte MG, van der Heide UA, Pos FJ, Lebesque JV, van Herk M, Incrocci L, Heemsbergen WD. Dose–surface maps identifying local dose–effects for acute gastrointestinal toxicity after radiotherapy for prostate cancer. Radiotherapy and Oncology 2015; 117; 515-520.

[11] Peterson JL, Buskirk SJ, Heckman MG, Diehl NN, Bernard JR Jr, Tzou KS, Casale HE, Bellefontaine LP, Serago C, Kim S, Vallow LA, Daugherty LC, Ko SJ. Image-guided intensity-modulated radiotherapy for prostate cancer: Dose constraints for the anterior rectal wall to minimize rectal toxicity. Medical dosimetry 2014; 39(1):12-7.

[12] Smeenk RJ, Hoffmann AL, Hopman WPM,Th. van Lin ENJ, Kaanders JHAM,. Dose-effect relationships for individual pelvic floor muscles and anorectal complaints after prostate radiotherapy. Int J Radiat Oncol Biol Phys 2011; 83(2): 636-644.

[13] Petersen E, Bregendahl S, Langschwager M, Laurberg S, Brock C, Drewes A, Krogh K, Hoyer M, Lundby L. Pathophysiology of late anorectal dysfunction following external beam radiotherapy for prostate cancer . Acta Oncologica 2014; 53(10): 1398–1404.

[14] Fernández-Fraga X1, Azpiroz F, Malagelada JR et al. Significance of pelvic floor muscles in anal incontinence. Gastroenterology 2002; 123(5):1441-50.

[15] Rostaminia G, White D, Quiroz LH, et al. 3D pelvic floor ultrasound findings and severity of anal incontinence. Int Urogynecol J. 2013; 25(5):623-9.

[16] Ebert MA, Foo K, Haworth A, Gulliford SL, Kennedy A, Joseph DJ, Denham JW. Gastrointestinal dose-histogram effects in the context of dose-volume-constrained prostate radiation therapy: analysis of data from the RADAR prostate radiation therapy trial. Int J Radiat Oncol Biol Phys 2015; 91(3):595-603.

[17] Cicchetti A, Rancati T, Ebert M, Fiorino C, Palorini F, Kennedy A, Joseph DJ, Denham JW, Vavassori V, Fellin G, Avuzzi B, Stucchi C, Valdagni R. Modelling late stool frequency and rectal pain after radical radiotherapy in prostate cancer patients: Results from a large pooled population. Phys Med. 2016; 32(12): 1690-1697.
[18] Pavy JJ, Denekamp J, Letschert J, et al. EORTC Late Effects Working Group. Late effects toxicity scoring: The SOMA scale. Radiother Oncol 1995; 35:11–15.
[19] van der Laan HP, van den Bergh A, Schilstra C, et al. Grading-system-dependent volume effects for late radiation-induced rectal toxicity after curative radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2008; 70:1138–45.
[20] Takemoto S, Shibamoto Y, Ayakawa S, Nagai A, Hayashi A, Ogino H, Baba F, Yanagi T, Sugie C, Kataoka H, Mimura M. Treatment and prognosis of patients with late rectal bleeding after intensity-modulated radiation therapy for prostate cancer. Radiation Oncology 2012; 7:87.
[21] Norton C, Cody JD. Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults. Cochrane Database Systematic review 2012; 11;(7): CD002111.
[22] Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, McGuire DB, Migliorati C, Nicolatou-Galitis O, Peterson DE, Raber-Durlacher JE, Sonis ST, Elad S; Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014; 120(10):1453-61.
[23] Nascimento M, Aguilar-Nascimento JE, Caporossi C, Castro-Barcellos HM, Motta RT. Efficacy of synbiotics to reduce acute radiation proctitis symptoms and improve quality of life: a randomized, double-blind, placebo-controlled pilot trial. Int J Radiat Oncol Biol Phys 2014; 90(2): 289-95.
[24] Foroudi F, Pham D, Bressel M. et al. Intrafraction bladder motion in radiation therapy estimated from pretreatment and posttreatment volumetric imaging. Int. J. Radiation Oncology Biol. Phys 2013, pp 86(1):77-82.
[25] Hathout L, Folkert MR, Kollmeier MA et al. Dose to the bladder neck is the most important predictor for acute and late toxicity after low-dose-rate prostate brachytherapy: implications for establishing new dose constraints for preatment planning. Int. J. Radiation Oncology Biol. Phys. 2014; 90(2), 312-319.
[26] Ghadjar P, Zelefsky MJ, Spratt DE et al. The impact of dose to the bladder trigone on long-term urinary function after high-dose intensity-modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2015; pp. 88(2): 339–344.
[27] Ahmed AA, Egleston B, Alcantara P et al. A novel method for predicting late genitourinary toxicity after prostate radiation therapy and the need for age-based risk-adapted dose constraints. Int J Radiat Oncol Biol Phys 2013; 86(4):709-715.
[28] Harsiola A, Vargas C, Yan D et al. Predictors for chronic urinary toxicity after the treatment of prostate cancer with addaptive three-dimensional conformal radiotherapy: dose-volume analysis of a phase II dose-escalation study. Int. J. Radiation Oncology Biol. Phys 2007; 69(4): 1100–1109.
[29] Scobioala S, Kittel C, Wissmann N, Haverkamp U, Channaoui M, Habibeh O, Elsayad K, Eich HT. A treatment planning study comparing tomotherapy, volumetric modulated arc therapy, Sliding Window and proton therapy for low-risk prostate carcinoma. Radiation Oncology 2016; 11(1):128.
[30] Yeo I, Nookala P, Gordon I, Schulte R, Barnes S, Ghebremedhin A, Wang N, Yang G, Ling T, Bush D, Slater J, Patyal B. Passive proton therapy vs. IMRT planning study with focal boost for prostate cancer. Radiation Oncology 2015; 10:213.
[31] Palorini F, Botti A, Carillo V et al. Bladder dose-surface maps and urinary toxicity: Robustness with respect to motion in assessing local dose effects. Physica Medica 2016, 32(3): 506-11.
[32] Steiner MS. The puboprostatic ligament and the male urethral suspensory mechanism: an anatomic study. Urology 1994, pp44(4):530-4.

[33] Bacon CG, Giovannucci E, Testa M, et al: The association of treatment-related symptoms with quality-of-life outcomes for localized prostate carcinoma patients. Cancer, 2002; 94(3): 862-71.
[34] Thor M, Olsson CE, Oh JH, Alsadius D, Pettersson N, Deasy JO, Steineck. Radiation Dose to the Penile Structures and Patient-Reported Sexual Dysfunction in Long-Term Prostate Cancer Survivors. J Sex Med. 2015; 12(12):2388-97.
[35] Cozzarini C, Rancati T, Badenchini F, Palorini F, Avuzzi B, Degli Esposti C, Girelli G, Improta I, Vavassori V, Valdagni R, Fiorino C. Baseline status and dose to the penile bulb predict impotence 1 year after radiotherapy for prostate cancer. Strahlenther Onkol. 2016; 192(5):297-304.
[36] Yahya N, Ebert MA, Bulsara M, Kennedy A, Joseph DJ, Denham JW. Independent external validation of predictive models for urinary dysfunction following external beam radiotherapy of the prostate: Issues in model development and reporting. Radiother Oncol. 2016; 120(2): 339-45.
[37] Schwarz M, Pierelli A, Fiorino C, Fellin F, Cattaneo GM, Cozzarini C, Di Muzio N, Calandrino R, Widesott L. Helical tomotherapy and intensity modulated proton therapy in the treatment of early stage prostate cancer: a treatment planning comparison. Radiother Oncol. 2011 ; 98(1) :74-80.

Nederlandse samenvatting

Introductie

In dit proefschrift wordt allereerst het verloop van de kwaliteit van leven van prostaatkankerpatiënten die behandeld worden met radiotherapie onderzocht. Daarnaast is onderzocht welke bijwerkingen de grootste impact hebben op de kwaliteit van leven en als laatste zijn twee NTCP modellen gemaakt om de kans op bijwerkingen op basis van dosis te voorspellen.

Belangrijkste bevindingen

In **hoofdstuk 2** wordt het verschil in kwaliteit van leven tussen prostaatkankerpatënten en een normatief cohort onderzocht. In deze longitudinale case-control studie tonen we aan dat de kwaliteit van leven van patiënten behandeld met radiotherapie lager is dan voorafgaand aan de behandeling en lager dan de kwaliteit van leven van het normatieve cohort. Aanvullende analyses lieten zien dat comobiditeit zoals hartaandoeningen en COPD een invloed hebben op het verloop van deze afname.

In **hoofdstuk 3** zijn de mogelijke oorzaken voor de afname in kwaliteit van leven na radiotherapie onderzocht. De impact van bijwerkingen op de kwaliteit van leven is geanalyseerd gebruikmakend van een multivariate analyse. Zowel gastrointestinale als genitourinaire toxiciteit hadden een significante invloed op de kwaliteit van leven van deze patiënten na afloop van hun behandeling.

In **hoofdstuk 4** is de relatie bepaald tussen gastrointestinale klachten en dosisvolume parameters in en direct rondom het anorectum. Verschillende klachten waren geassocieerd aan verschillende anatomische substructuren; rectaal bloedverlies was gerelateerd aan hoge dosis aan het anorectum als geheel en bloedverdunners, incontinentie was gerelateerd aan de dosis aan de externe anale sfincter en musculus iliococcygeus. Defecatie frequentie was gerelateerd aan intermediaire doses aan de musculus levator ani.

In **hoofdstuk 5** zijn de dosis-volume paramters van de blaas gerelateerd aan genitourinaire klachten. Verschillende bijwerkingen waren geassocieerd met verschillende anatomische substructure in de blaas; incontinentie voor urine was geassocieerd aan de gemiddelde dosis aan het trigonum, terwijl haematurie gerelateerd was aan de dosis aan de blaaswand en hartaandoeningen. Dysurie was gerelateerd aan hoge dosis aan het trigonum en een ziektegeschiedenis waarbij een TURP is uitgevoerd.

Dankwoord

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Arjen van der Schaaf. "Ik run wel even het script met deze selectie van de variabelen". Die zin hebben we vaak besproken. Daar waar je me hebt laten zien hoe in Matlab een door bootstrapping gecorrigeerd model theoretisch gezien werkt, heb ik zelf in R laten zien dat ik dat ook kan. Dat laatste was niet mogelijk geweest zonder jouw soms (maar zeker niet altijd) relatief eenvoudige weergave van ingewikkelde wiskundige modellen. Als we kijken naar mijn onderzoek, durf ik met 95% betrouwbaarheid te zeggen, dat ondanks dat we relatief weinig besprekingen hebben gehad, de richtingscoefficiënt van mijn leercurve tijdens deze meetings met jou het stijlst was, heel veel dank daarvoor!

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Hans Paul. Het begon als kamergenoten, maar uiteindelijk hebben we toch vele "hobby's" gedeeld, waarbij jij over het algemeen iets intensiever betrokken was dan ik. Vage gesprekken over statistiek, squash, goede koffie zetten en geocaching waren gemeenschappelijke interesses, waarin jij soms iets beter was dan ik en andersom (ik ben inmiddels alweer vergeten hoeveel gram je van welke boon je ook weer moest nemen voor de perfecte espresso, kun je me binnenkort weer even bijpraten over de nieuwste ontwikkelingen?). Ik ga ervan uit en hoop je nog vaak te mogen spreken over al bovenstaande!

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Over de auteur

Wouter Schaake is geboren op 7 juli 1981 te Utrecht. Op zijn 11e ging hij naar het Stedelijk Gymnasium te Breda, wat hij afrondde in 1998 en direct met de studie psychologie begon aan de RijksUniversiteit Groningen. Na het afronden van zijn doctoraal studeerde hij via het zij-instroom traject van de RuG Geneeskunde en rondde daar het bachelorprogramma af in 2007. Na een paar jaar ondernemer te zijn geweest besloot hij het onderwijs in te gaan en werd in 2009 docent aan de Hanzehogeschool Groningen bij de opleiding Medisch Beeldvormende en Radiotherapeutische Technieken (MBRT). Sinds 2017 geeft hij ook les aan de Masther Healthy Ageing Professional en aan de Master Physician Assistant.

Momenteel werkt Wouter nog steeds als docent en onderzoeker aan de Hanzehogeschool Groningen, waarin hij met name lesgeeft in anatomie en onderzoeksvaardigheden. Daarnaast is hij sinds 2018 lid van de Hanze Ethisch Advies Commisse (HEAC).

Wouter heeft twee zoons, Hugo en Tom en woont samen met zijn vriendin Maartje en haar kinderen Mees en Thijs in het Groningse Noordhorn.